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ENDOCRINE DISORDERS

BY

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DIRECTOR OF THE MEDICAL CLINIC, UNIVERSITY OF ROSTOCK i. M.

WITH AN INTRODUCTION BY

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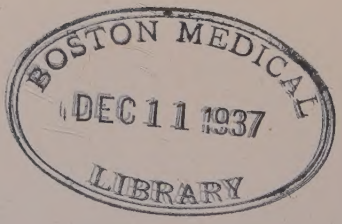
HUMPHREY MILFORD

OXFORD UNIVERSITY PRESS

London Edinburgh Glasgow Leipzig
New York Toronto Melbourne Cape Town
Bombay Calcutta Madras Shanghai

1929

14. K. 62.



Printed in Great Britain by R. & R. Clark, Limited, *Edinburgh.*

FOREWORD

Endocrinology, fifty years ago a small, neglected appendage to clinical medicine, is to-day becoming universally recognized as vitally important for physiopathologist and clinician alike. A glance at a copy of any medical journal will show that it has also become a fashion, and specialists of every branch industriously unite in studying the problems of internal secretion.

The growth of knowledge gained in the fields of clinical, anatomical and experimental endocrinology is so rapid that the standard text-books fail entirely to keep up with it. The sections they devote to the subject are very meagre in comparison with those that bear the dignified, old-established headings of Circulatory, Alimentary System, and the like. On the other hand, the new monographs overburden the practitioner with more experimental data in normal and morbid physiology then he can possibly assimilate. Therefore, when I was asked to write a book on endocrine disorders that should be primarily clinical and practical, I accepted the invitation with great pleasure. Quite obviously this little volume cannot deal with the whole gigantic literature of endocrinology. On the other hand, it is designed as a clinical manual grounded on a rather wide personal experience, that will give the theoretical as well as the practical reader what he chiefly requires : pathogenesis, symptomatology and treatment.

H. CURSCHMANN.

Rostock, *October* 1927.

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INTRODUCTION

It is unfortunately impossible in this book to treat the anatomical and physiological bases of endocrinology with the thoroughness that their importance and complexity deserve. Our terms of reference confine us to those aspects which are essentially practical. The normal and pathological physiology of the endocrine glands will therefore, as a rule, be considered alongside the description of the clinical pictures of endocrine disorders.

Glands of internal secretion, or *endocrine glands*, are those of which the function, wholly or partially, is to secrete specific substances, known as hormones, into the bloodstream. Some of the endocrine glands, therefore, possess no excretory ducts ; examples of these are the adrenals, thyroid, parathyroid, pineal and thymus. Others, such as the gonads, pancreas, liver and intestine, possess an external as well as an internal secretory function, and are provided with excretory ducts.

These hormones are not protein bodies, have no fermentative characteristics, and can act only on living cells, and their action is in some way quantitative (Falta).

The question as to which organs of the body possess internal secretory functions has not yet been answered with any certainty. There is no doubt that the thyroid, parathyroid, thymus, pituitary, adrenals, the islets of the pancreas, and the male and female gonads all possess them, but the endocrine function of the pineal has recently come anew under suspicion. Besides these organs it is certain that many others also have a more or less distinct endocrine function, even if the evidence for this function is not gener-

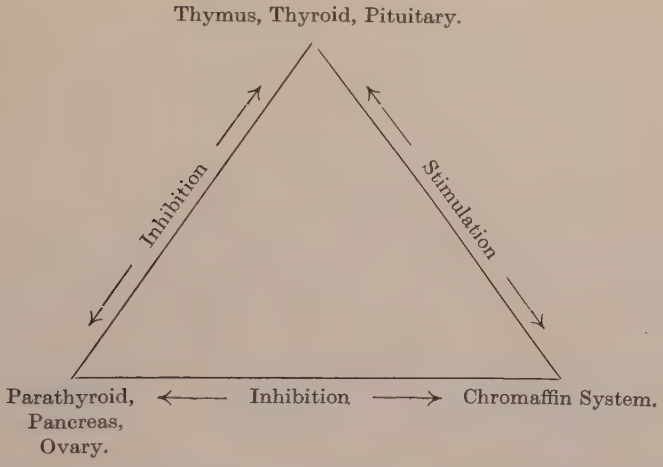
ally regarded as conclusive. Hormonopoietic properties have been ascribed not only to the liver, spleen and bone-marrow, but even to the skin and heart. Modern physiologists, going even further, ascribe endocrine functions to almost every tissue or organ in the animal body, and it is certainly true that nearly all tissues excrete into the blood, as part of their function, substances which may have some kind of regulating action on some of the life-processes. Falta was right, however, when he strongly advised the doctor to avoid an undefined system of this kind and for the purpose of the practical study of disease to adhere for the time being to the already existing concepts of "incretology".

The only hormones with a known chemical composition are those of the adrenals (adrenalin), the thyroid (thyroxin), and the bowel (cholin). The active principle of the islets of the pancreas has of late been recognised and studied, at least biologically, under the name of insulin ; and the same applies to the recently isolated parathyroid secretion and to the hormone of the infundibular apparatus of the hypophysis (pituitrin).

The action of these organs and their hormones was originally investigated in man after operation or during illness, and especially in patients whose parathyroids had been removed with the thyroid, who had been castrated, or who had suffered damage to their adrenals through disease. The normal and morbid physiology of the endocrine glands was founded on human experiment. It was supplemented and amplified by work on animals, which showed not only the failure of function that followed extirpation but also its return, even in excessive degree, when glands were implanted or hormones were administered in prepared form.

In the normal as in the diseased organism there is an extraordinary functional correlation between the different endocrine organs. These correlations are so close and universal that it is often difficult to say in a given case of endocrine disorder which unit was originally at fault. Various authorities have claimed to be able to distinguish some of the rules governing these correlations. For example, it has

been correctly observed that an inhibition of the gonadal function is the normal pathological consequence of a failure of the thyroid or hyperactivity of the pituitary.



The accompanying diagram shows Dr. B. Aschner's attempt to systematize the opposite effects of the endocrine organs on one another. Although his plan of treating the pituitary as a single body and bracketing it for correlative purposes with the thymus may arouse some misgiving, Aschner's scheme holds good in a great many relationships, especially in animal experiments. Human pathology, however, is always reminding us that schemes of this kind, taking no account of the variability of the action of the glands, are constantly being infringed. Moreover, so meticulously have these correlations been investigated and re-investigated that some authorities now no longer acknowledge disturbances of single glands (monoglandular disorders) but incriminate a whole group of glands simultaneously (pluriglandular disorders). In rushing from the monoglandular extreme, which made things a little too simple, to the pluriglandular opposite they have at times undoubtedly weakened the foundations of glandular therapy.

In face of exaggerated ideas as to pluriglandular disorders it must nevertheless be noted that many nervous

affections, especially myopathies (such as myotonic dystrophy, myotonia, Erb's muscular dystrophy, and others), autonomic "neuroses" (sclerodermia, Raynaud's disease, erythromelalgia), blood diseases (hæmolytic jaundice, Biermer's anæmia, etc.), many vitamin-deficiency diseases (rickets, scurvy), and other disease-groups, are associated with more or less regular and protean pluriglandular symptoms. It is, however, inadmissible, because unproven, to ascribe wherever possible an exclusive pathogenic significance to these symptoms. Sophistry of this kind is apt to, and often does, meet its deserts in therapeutic disappointments.

The endocrine organs and their hormones exert very profound and multifarious effects. They influence the whole metabolism ; the nervous system, especially the vegetative, and the psyche ; and the growth and stature of the body and every part of it, as is shown so strikingly in the influence of the gonads and thyroid on the skeleton, the growth of hair and the deposit of fat. The endocrine system is therefore undoubtedly of great, perhaps exclusive, import in the building up of the physical and psycho-autonomic constitution of the individual. This is a fact which the gross extravagances of certain authorities have not succeeded in controverting, and the reality of which every experienced physician immediately senses and recognizes when he hears, for example, of hypo- and hyperthyroid or eunuchoid types or constitutions.

It is correct, when considering the widespread and profound action and counteraction of the endocrine glands and their hormones, to speak with Falta of a *hormonopoietic system*. We know that the hormones act chiefly upon the sympathetic and parasympathetic systems and all the organs which they innervate. Their influence extends even to the electrolytic constellation of the cell, the marked effect of which on the sensitivity of the vegetative nervous system is well known. If potassium ions are in excess the parasympathetic is stimulated ; if calcium ions, the sympathetic. The constant influence of the electrolytes on the organs of the body also, however, makes the effect of the hormones on them a very important one ; for example, potassium ions

increase the efficacy of the thyroid hormone and calcium ions diminish it. Similarly, the power of adrenalin to raise the blood-pressure is intensified when calcium ions are expelled to make room for potassium ions, and reduced when the potassium ions predominate.

This hormonopoietic system obviously becomes still more complicated if its relations with the vegetative nervous system and its centres are traced further. On the one hand, the hormones stimulate the sympathetic-parasympathetic ; on the other, the endocrine glands are excited to pour out their secretions through the stimulation of this system by, for instance, psychological reactions or exogenous toxins. Finally, there is no doubt that the whole endocrine system, so far from being an anarchy, is governed by higher cerebral centres; in fact, by centres in the hypothalamic portion of the mid-brain. These mesencephalic centres, among which are also those of the sympathetic and parasympathetic, constitute the cerebral projection-fields of the endocrine organs, the central keyboard on which the hormonopoietic stimuli play their melodies. This territory has also been shown to contain centres for heat-regulation, sugar-transformation, water and salt excretion, fat and mineral metabolism, the sexual and many other functions.

Knowledge of these mesencephalic projection-fields, and the observed fact that clear clinical pictures of endocrine disorder may be manifested without any disease of the gland or glands concerned, in demonstrable lesions of the mid-brain (cf. the pure cerebral forms of apparently pituitary obesity, diabetes insipidus, acromegaly and Simmonds' cachexia) have led many workers of late to attack the whole structure of the theory of the causation of endocrine disorders. Some have, for instance, denied to the pituitary any connection with diabetes insipidus or dystrophia adiposo-genitalis. However important it may be always to bear in mind the existence of the cerebral keyboard of the endocrine system, it seems to me—from the practitioner's point of view—that that attitude tends to discredit the present system of endocrine diseases in favour of the mesencephalic centres. If we hold our ground on clinical fact, we shall always remember

that without the elementary monoglandular standpoint from which Moebius, Kocher and others explained the thyroidal origin of Graves' disease and myxœdema, we should possess no effective cure for those gravest of endocrine disorders.

SECRETORY DISORDERS OF THE THYROID

Anatomy and Physiology.—The normal human thyroid consists of two symmetrical lobes lying close to the trachea, sometimes to the larynx, and joined by a small glandular bridge known as the isthmus. The thyroid is very vascular, and is innervated from the sympathetic and parasympathetic. Normally it is a soft and unobtrusive structure, difficult to palpate and not clearly visible. Its glandular tissue is built up of follicles lined with cylindrical and cubical epithelium containing fluid colloid ; this holds the specific internal secretion, which reaches the blood by the lymphatic channels.

The female thyroid often undergoes a physiological swelling during menstruation and pregnancy. The quantity and effect of the internal secretion probably correspond with the colloid content. It is extraordinarily rich in iodine, which is present in the form of iodo-thyro-globulin (Baumann, Oswald). Kendall has recently succeeded in isolating the active principle under the name of thyroxin, a tri-iodotryptophane ; it is thus proved to consist of a number of distinct fractions possessing distinct properties. In 1926, Harington discovered a method of isolating thyroxin, and subsequently a means of producing the hormone synthetically (Thyroxin Rothe).

The thyroid hormone has a marked influence on the vegetative nervous system, especially—either directly, or indirectly in conjunction with adrenalin—on the sympathetic and the organs it supplies, and also on the whole metabolism. Its effect on the interchange of gases is especially striking : an increase in secretion accelerates and a decrease slows the process. The effects of thyroxin on the individual, for instance its influence on the development of bone and genital organs and on the metabolism of nitrogen, glycogen, water and salt, are evident in the physiopathology of hyper- and hypothyroidism.

We do not propose to discuss those disorders or pathological

changes in the thyroid which have been shown by experience never, or only exceptionally, to give rise to typical general endocrine syndromes. For instance, we shall deal under the next heading with common goitre, either in the diffuse or nodular form, only in its relations with hyperthyroidism or dysthyrosis. Nor are we concerned with the neoplasms of the thyroid, such as carcinoma, sarcoma and their sequelæ, nor the various forms of thyroid inflammation which are associated with so many acute and chronic infections. We are obliged to confine ourselves to the typical general disorders of thyroidal origin, which we propose to classify, in accordance with established custom, under the heads of hyperthyroidism on the one hand, and hypo- or athyroidism on the other. It will be seen that all their individual symptoms bear a diametrically opposite relationship one to another.

Diseases due to Excess of Thyroid Secretion (Hyperthyroidism)

Mœbius has distinguished two forms—a primary and a secondary—of Graves' disease (exophthalmic goitre), which was previously regarded as a single entity. The primary, he says, corresponds with the " Vollbasedow " of Kocher, the secondary with the incomplete forms, *i.e.* a simple goitre that has become " Graves " in type. Other authors, again, have distinguished from these the form due to the therapeutic administration of iodine, and the " formes frustes " (" Basedowoid "), or incomplete Graves' disease. Chvostek, Sudek and others recommend the following classification :

(i) Classical Graves' disease, a dysthyrosis.
(ii) " Thyroidismus ", a simple accentuation of the function of the gland.
(iii) Status neuropathicus with one or more Basedowoid features.

To my mind this distinction is neither clinically nor anatomically sound, because, as the recent work of Helwig and Holst has shown, these forms pass readily from one into another. The classification I have quoted is physio-pathologically untenable, because the essential metabolic, circula-

tory and other symptoms show the same tendency to ready transition between the different groups. I prefer to regard them from a unitary standpoint, even with regard to the " primary " and " secondary " forms, the manifestations of

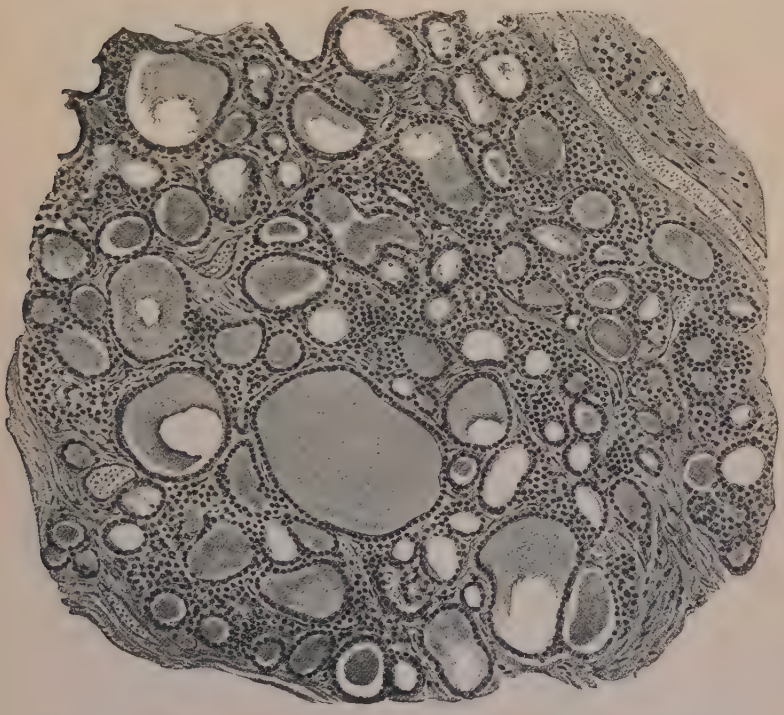


Fig. 1 (*a*).—Normal Thyroid with Colloid Formation. (After Falta.)

which are identical, and so I am discussing the hyperthyroses as a whole under the heading of Graves' disease.[1]

Graves' Disease

This disease was first discovered by Parry in 1786, but was made generally known by Graves in England and by the Merseburg physician, Basedow, in 1840.

[1] Translator's Note.—According to the usual custom in this country, the term " Graves' disease " has been substituted generally for the original " Basedow's disease."

Its *chief symptoms* are tachycardia; a rise in the gaseous interchange and a secondary increase of the protein metabolism, with a corresponding loss of weight; goitre (generally pulsating); exophthalmos, with the signs of Græfe and Stellwag; psychic symptoms, such as heightened sensitivity to stimuli; tremor, muscular weakness, hyperidrosis, cutaneous changes, falling of hair and diarrhœa.

Incidence.—Six females are affected for every male;

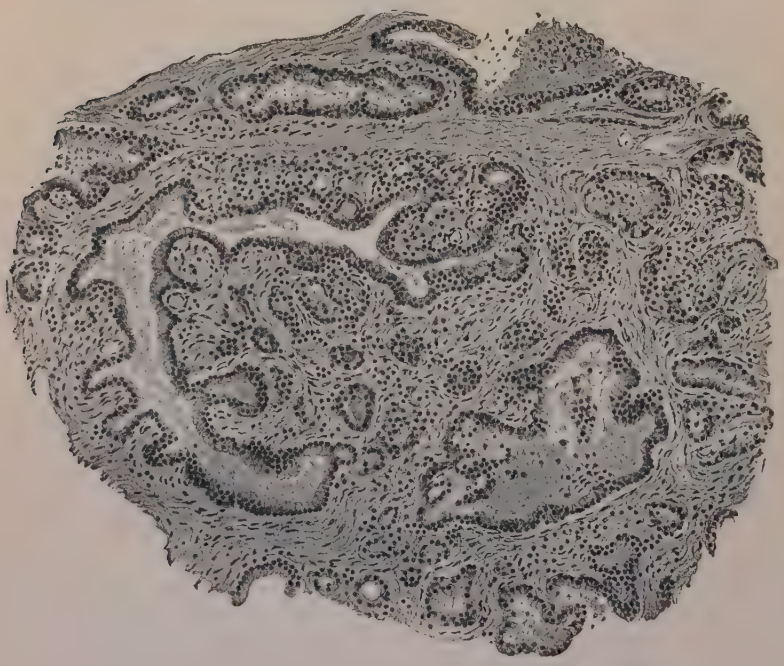


Fig. 1 (*b*).—Thyroid in Graves' Disease. (After Falta.)

children and persons over sixty seldom suffer. The disease usually begins between the twentieth and fortieth years. It is uncertain whether the mortality is greater in goitrous regions; I do not think it is.

Ætiology.—It is certain that the rôle of the constitution is a very important one. "Basedow families" are often reported. A neuropathic disposition, especially one in which the vegetative system is at fault, is frequently part of the

picture ; occasionally the outbreak of Graves' disease is merely the culmination of psychopathic and sympathicotonic disturbances of many years' standing. It is probable that outside factors help to bring about this climax ; psychic troubles, such as worry, grief and even sexual abstinence, are incriminated. Infections such as typhoid, influenza, malaria, polyarthritis and syphilis, or local inflammation, have been known to usher in Graves' disease. Pregnancy and the climacteric may accentuate the complaint, but in my experience they generally diminish it. I consider the therapeutic administration of iodine to be a very important factor, especially in menopausal patients with old goitres. A goitre that has been harmless for a long time may change to the Graves' type, either spontaneously or from exogenous injury, even if no iodine is taken ; often, but not invariably, without evoking the typical ocular syndrome.

Course.—The disease generally begins insidiously, especially in mild cases ; the virulent type with an acute fulminating outbreak is rare. When the onset is slow, the first symptoms to appear are general symptoms of neurosis, such as hysteria, hypomania and neurasthenia. Alongside these appear cardiac symptoms, and the patients notice the thyroid swelling and their friends observe the eye changes. These are followed by a host of other dystrophic and vegetative disturbances.

Symptomatology.—From the practical point of view, the *heart symptoms* are the most important, especially the almost constant tachycardia, which is persistent and not merely evoked by psychical stimuli, though of course these may accentuate it. The pulse-rate is usually 120-140, extremely rarely 200 ; very occasionally " vagotonic " cases have been reported with a normal or subnormal pulse-rate. The pulse is usually regular, and arrhythmia is only encountered in advanced cases with cardiac insufficiency. The heart is usually enlarged, and its action, especially the apex-beat, lively ; systolic bruits are sometimes heard. The great vessels pulsate abnormally strongly and visibly. The pulse is generally weak but jumpy, and the systolic blood pressure is increased (140-160), while the diastolic is normal,

or, more often, lowered. H. Zondek found that in the electrocardiogram the auricular wave and oscillations were of an abnormal height with a low R wave ; this is the reverse of what is observed in myxœdema. Sudden heat-flushes, blushing, dermatographia and abrupt changes of colour are the typical vasomotor symptoms. These objective circulatory changes correspond with the subjective ones of palpitation and tremor of the heart, throbbing in the neck, head

Fig. 2.—Fully developed Graves' disease. A woman of 30 who subsequently died. (Author's case.)

and limbs, anginal pain and shortness of breath. Together with other nervous symptoms, they may exist for a relatively long time before the patient complains of the most alarming symptom of all, the exophthalmos.

The *ophthalmic symptoms* begin with a relatively inconspicuous brightness of the eyes, but exophthalmos soon shows itself in " goggle eyes ", generally bilateral, but less often asymmetrical. The tension of the ocular bulb is normal, and there is no pulsation. The great distance between the lids and the abnormal infrequency of winking constitute

Stellwag's sign, which is always present. When the patient looks downwards the upper lid does not sufficiently follow the sinking of the eyeball, and a band of white sclera is left visible between lid and cornea (von Græfe's sign). Mœbius' sign—insufficient convergence—is not specific, and is therefore unimportant. Conjunctivitis is another frequent eye symptom, but ocular palsies, optic neuritis and optic atrophy are fortunately rare. As a rule, ocular movement, vision, light-reaction and fundus oculi are normal. A drop of adrenalin in the conjunctival sac of one eye will bring about a more or less pronounced mydriasis of the pupil (Loewe's sign).

In the " Merseburg Triad ", the triple syndrome on which Basedow used to rely long ago, the third symptom, after tachycardia and exophthalmos, was *goitre*, which we accept to this day as the most important pathogenetic symptom. According to Sattler the goitre is absent (on palpation) in only 6 per cent of cases. It usually develops slowly to a regular, comparatively small goitrous formation, seldom larger than three times the size of the normal gland. Often only one lobe, usually the right, is enlarged. The onset of this goitre is rarely rapid, but may be so in acute, virulent cases. The goitre of Graves' disease is recognizable by its vascularity ; it pulsates vigorously, and arterial thrill, and sometimes venous murmur, are audible and palpable in it. Owing to its softness it rarely sets up pressure-effects.

The thyroid in a case of old parenchymatous goitre that has changed into Graves' disease differs from the typical goitre in being larger, harder and less vascular.

Anatomically, the goitre of Graves' disease is a hyperplasia of the large follicles, *i.e.* a diffuse colloid goitre. Its development corresponds with the severity of the case, and proceeds by liquefaction of the colloid, proliferation of the epithelial cells and the multiplication of blood-vessels of every kind. A. Hellwig also found changes of this kind in the nodular goitre ("struma nodosa Basedowificata") of T. Kocher.

Other glands besides the thyroid are naturally involved, and the most frequent and important of such complications is hyperplasia of the thymus. The pituitary often suffers

cystic change, and the adrenals, pancreas, parathyroids and, especially, the gonads are also liable to various modifications, all of which give rise to appropriate symptoms. Involvement of the lymphatic glands and of the spleen and liver has been observed, but rarely. After the " symptom-triad " of Basedow (tachycardia, exophthalmos and goitre), the picture is dominated by the *nervous symptom-complex*, both subjective and objective. The best-known sign is the fine tremor of the extended fingers and hands ; less frequently the head, legs or trunk are affected. More distressing for the patient, however, is the weakness of his or her muscles, especially those of the legs, and the readiness with which they become fatigued. This debility is often extreme, and may lead to definite intermittent genu valgum and falling. Real paralyses are, however, very rare. In addition to tremor and weakness there is often a greater or lesser degree of hurry, restlessness and lack of co-ordination of movement, which may sometimes be reminiscent of chorea. The only disorders of sensation are neuralgic pains and a general feeling of heat. The tendon-jerks are usually accentuated, but the excitability of the motor nerves is not increased.

The most important of the nervous disturbances are the *psychological changes*. In her mind as in her body, the patient undergoes a complete change—almost, as the saying goes, " so that her best friend would not know her again "—and never for the better. The disorder is chiefly one of the affect and character, and mirrors faithfully the altered motor state. The psychic condition of the Graves' patient is characterized by restlessness, conflict and heightened sensitivity in every direction. She becomes melancholy, suspicious, shy, capricious, unreliable and not infrequently childish and silly. In short, a good-natured and useful woman can turn into her own absolute opposite. In addition there supervene, to the patient's social detriment, a psychasthenia, forgetfulness and distraction that simulate a regression to a primitive type of intelligence. Sometimes, especially in a woman, an excessive sexual susceptibility shows itself in tasteless and unsightly coquetries of dress and manner which contrast with her pitiable appearance in

a way that would be comic if it were not tragic. True psychoses are rare, but in acute and pernicious cases they may take the form of delirium, confusion or mania. Stuporose, lethargic and negativistic states are even rarer. It must be noted, however, that in incomplete cases there may be no conspicuous psychic symptoms.

Disturbances of metabolism, as far as we know at present, are never absent. They express themselves most strikingly in an emaciation, which may be extreme. I have seen a stout woman lose 105 lb. in nine months. Patients often give a history of losing 20-40 lb. in a short time. Diagnostically the most important change is the rise in the gaseous interchange and in the basal metabolic rate, which may become as high as 90 per cent. The following table provides a characteristic example :

MARRIED WOMAN, AGED 31

Date.	Consumption of Oxygen.	Excretion of Carbon Dioxide.	Respiratory Quotient.	Actual Calorie Consumption.	Calculated Calorie Consumption (Benedict-Harris).	Rise.
1926.	c.cm.	c.cm.				per cent.
June 21	312·016	265·408	0·878	2223	1287	77
,, 26	304·788	277·080	0·909	2183	1273	74
July 22	313·25	296·24	0·94	2258	1263	78
Aug. 27	289·792	253·568	0·874	2061	1244	65
Sept. 24	309·276	290·532	0·93	2226	1254	77
1927						
Apr. 2	361·50	278·22	0·70	2512	1310	92

The patient was a bad case of typical Graves' disease who, on account of her extreme terror of operation, was treated by X-rays, which only slightly improved her basal metabolic rate and general health. After that she underwent an ill-advised "treatment", as a result of which her basal metabolic rate went up to the enormous figure of +92 per cent. An operation was performed but was too late to be of any use, and she died on the following day.

In addition to the disorder of the whole process of oxidation there is a disorder of the protein metabolism,

which shows itself in a nitrogen defect, even when an ample or an excessive supply of proteins and total calories is maintained. Frau Müller held that the rise in oxidation was primary and the rise in protein metabolism secondary. The fat- and sugar-metabolisms also pay toll. Some Graves' patients, it is true, remain relatively plump or become so after a short course of treatment, but they are always persons who have a relatively small rise in the basal metabolic rate, and who, apart from their present malady, show a tendency to hypothyroidism. Glycosuria, whether true diabetes or merely alimentary, is especially frequent in Graves' disease families. Most patients respond to adrenalin injection with an abnormal rise in the blood-sugar and often with glycosuria. Polyuria without sugar is rare.

The *temperature* is usually normal, but may sometimes be rather high. In the so-called " Basedow fever " continued rectal temperatures of 99°-100° F. have been recorded. As I have already mentioned, the subjective sensation of excessive heat is a common and troublesome symptom.

The *respiratory organs* rarely show changes, and even so the changes are not characteristic. It is asserted that tuberculosis is frequently associated with true Graves' disease ; I have never seen it, but I have occasionally seen Graves' disease associated with bronchial asthma, and have often seen marked symptoms of Graves' disease develop during attacks of asthma. Once I even observed plastic bronchitis in a patient with severe Graves' disease.

Trophic and secretory, as well as vasomotor symptoms are frequently in evidence. General or regional hyperidrosis, the commonest of them, is not confined to night-sweats but may appear by day. The skin is very vascular and moist and exceptionally thin and delicate, like that of a small child. The hand of a Graves' patient shows this peculiarity very clearly. Anomalies of pigmentation, chloasma, accumulation of pigment and vitiligo are common, but nail changes are rarer. Loss of hair, especially from the head, is almost invariably present, though it hardly ever progresses to complete baldness. This and early greyness combine with the other physical damage to make the patient appear

to have aged early and rapidly. Transient œdema, especially of the eyelids, is fairly common.

The functions of the *stomach* and *bowels* are often disordered. Especially frequent is obstinate diarrhœa, which often begins as simple morning looseness. Typical fat-stools are far rarer, and are seen in exceptionally bad cases where there are signs of an associated pancreatic insufficiency. The diarrhœa may be for a time the only sign of the disease, and

Fig. 3.—A woman of 47 with Graves' disease, showing early senescence. A favourable result was obtained by the use of X-rays. (Author's case.)

the attacks often resist ordinary measures. Not so common, but no less serious, are the gastric disorders. Crises of vomiting may occur, sometimes so severe as to threaten life ; ulcers and signs of hyperacidity are less often observed. The appetite fluctuates between ravenousness and anorexia, and the gastric secretion is very variable ; there is generally achlorhydria or hypochlorhydria, but I have found hyperacidity and hypersecretion. The gastric motility is disturbed by severe spastic crises.

The *blood* exhibits typical changes. Genuine anæmia is not one of them, but according to Th. Kocher, leucopenia with some degree of lymphocytosis is common. The coagulation-time is lengthened and the iodine-content raised. The viscosity and protein-concentration of the blood serum are lowered, proportionately with the increased consumption of protein. (G. Deusch.)

The *skeleton* is not often involved. Osteomalacic softening of the bones has been observed in children with Graves' disease who showed great overgrowth. Kyphosis is rare. Marked chronic arthritis deformans occasionally supervenes as a genuine sequela of Graves' disease.

Pathogenesis.—Most of the symptoms depend upon the sympathetic system and the organs which it innervates, relatively few upon the parasympathetic. They are nearly all expressions of abnormal irritability. The cerebro-spinal system plays a less prominent part. The Graves' syndrome, which has its foundation in a constitutional or inherited neurotic disposition, used to be and still is often regarded as a primary vegetative and psychic neurosis. Nowadays, however, most authors agree with Mœbius that the chief part in it is played by the alterations in the function of the thyroid, the excessive (and possibly disordered) secretion of which acts directly or indirectly upon the vegetative nervous system and its organs. This view is supported on the one hand by the beneficial results of extirpation of the thyroid or its exposure to X-rays, and on the other by the fact that the reverse condition, myxœdema strumipriva, has a clinical picture diametrically opposed to that of Graves' disease in every respect. Moreover, a large number of Graves' symptoms can be brought on by the administration of thyroid preparations or of iodine. By reason of the linkage that is now known to exist between the various units of the endocrine system, changes in the functions of other glands (especially the thymus, and less often the pituitary and gonads) also play their part in the syndrome. Overactivity of the thymus is held responsible for the vagotonic symptoms. The intimate relation between the endocrine glands and the vegetative system ensures that in Graves'

disease the disorders of the two shall be co-ordinated into a systematic illness, to the detriment of both.

Treatment.—The first requisite is to reduce the function of the thyroid, and methods of treatment directed to any other ends are quite unreliable. For mild and medium-severe cases X-ray therapy is the most useful, but it demands the greatest accuracy in its use, and unremitting vigilance over its effects, particularly on the basal metabolic rate, to avoid overdosage and myxœdema. In severe cases and in those intolerant of X-rays the treatment of election, according to Kocher, is partial thyroidectomy ; he records success in 70-75 per cent, and a mortality rate of between 5 and 8 per cent, among selected cases. The operation should not be too long delayed. Relapses may occur after either method and demand a repetition of the treatment.

Rest and a suitable climate are also necessary. Patients often benefit from residence in moderate or high altitudes, but severe cases must be treated in an institution, and practically all have to give up their work. Physiotherapy is of little value, and excessive stimulation, as in carbon dioxide baths, is harmful. Pyschotherapy of all kinds has been tried ; it has no effect in severe cases, but every Graves' patient needs some psychological help in addition to treatment directed against the cause of the disease. Diet is important ; the reduction of morbidity and severity during the war years proved the correctness of early observations, such as those of B. F. Blum. The most necessary modification is the total or partial elimination of all substances rich in tryptophane, which is the basis of thyroxin : meat, milk, cheese, eggs and wheat are therefore to be avoided, but maize, rye, potatoes, vegetables and fruit are very poor in tryptophane. This fact deserves thought. Balint has cured genuine Graves' patients with suitable diet alone. Medication may be auxiliary or palliative, but rarely curative. It is well established, however, that iodine benefits many patients (Neisser), and the treatment with Lugol's solution instituted by Plummer is recommended by many authorities, especially before and after operation. Many more patients, on the other hand, will not tolerate iodine and get rapidly

worse on it. To distinguish which patients will benefit from iodine is as a rule only possible in a clinic where full and accurate observation of metabolism, weight and other factors can be made ; it is outside the usual scope of general practice, and I therefore do not advise the practitioner to try iodine on his Graves' patients. Ergotamine, the pure alkaloid of secale cornutum, has recently been recommended, and ergotamine tartrate, in the preparation marketed by Sandoz as " Gynergen " or " Femergen ", has given good results in doses of 0·5 c.cm., subcutaneously, twice or thrice daily. Arsenic and phosphorus preparations are useful, and many patients require sedatives such as valerian and bromides, or even adalin or luminal.

The tachycardia is not benefited by digitalis, but can sometimes be reduced by quinidine sulphate, 0·1–0·3 grm. thrice daily. For the obstinate diarrhœa the most effective drug is " pancreon " ; Von Domarus recommended adrenalin enemata. A " specific " treatment with Mœbius' " anti-thyroidin ", a serum prepared from lambs after the removal of goitre, has recently returned to favour. Insulin seemed to have no effect on my own patients, but other workers have reported better results, especially before operation.

Incomplete Forms of Graves' Disease

In my opinion there is no essential or hard-and-fast distinction between these and typical Graves' disease, any more than there is between the incomplete forms of other disorders, endocrine or otherwise, and their typical pictures (*e.g.* incomplete tabes or multiple sclerosis). They appear in various guises. Often an apparently incomplete form is really typical Graves' disease in its initial stage.

Among these " formes frustes " are :

(i) Subjective cardiac distress ; tachycardia with systolic hypertonia ; small but pulsating thyroid, but no eye signs nor sweats ; moderate psychic disturbances and slight loss of weight only.

(ii) Intractable diarrhœa ; slight tremor ; no heart or eye signs ; long-standing goitre ; psychic condition unimpaired.

(iii) Severe mental disorder of the manic-depressive or hysterical type ; marked loss of weight ; tachycardia ; slight goitre ; eye signs very slight or absent.

(iv) Long-standing goitre ; loss of weight after the menopause, whether or not iodine has been given ; severe subjective cardiac disturbances ; tachycardia ; no ocular triad, but sometimes brightness of the eye.

The last of these forms, which nearly always runs its course without the three signs in the eyes, occurs most frequently in elderly and middle-aged women with goitre, in which changes to the Graves' type have taken place. It corresponds to the previously mentioned "secondary form" (see p. 8) of Mœbius and Kocher.

To go to the root of the matter, however, the cardinal disturbance of metabolism, especially the rise in the basal metabolic rate, is common to all these forms, and a rise in protein metabolism (as shown by the lowered serum-protein concentration) is nearly always demonstrable. Also very general, though not quite so constantly present, is adrenalin mydriasis. The transformation of an old goitre into Graves' disease is also seen before and after pregnancy. The course and prognosis in such cases and the necessity for treatment are much the same as in typical Graves' disease.

It is correct to say of nearly all incomplete forms of hyperthyroidism that the **prognosis** for health is always very doubtful, and that they may become chronic if not properly treated. It is just this failure of misdiagnosed cases to improve and the invariable decline into terminal cachexia that makes it so necessary to broaden the diagnosis of hyperthyroidism to include "incomplete" and "atypical" forms of Graves' disease. It must be admitted, however, that these incomplete cases, even without treatment of the cause, show a substantially lower mortality rate than the typical ones, and a very low absolute mortality. It is practically impossible to give statistics on account of the difficulty of assigning accurate limits to the syndrome.

To sum up, the treatment of the incomplete forms should

not differ essentially from that of typical Graves' disease. I have never seen any striking or reliable improvements or cures follow symptomatic treatment, or treatment by drugs or electricity. I have found that X-rays gave the best results in my own incomplete cases, which have been very numerous, but naturally thyroidectomy will sometimes be necessary or desirable when for some reason a quick result has to be obtained or X-rays are contra-indicated. Diet, rest and—especially—psychotherapy are also important, as in the complete form.

Diseases due to Lack of Thyroid Secretion (Hypothyroidism)

Adult Myxœdema

The spontaneous myxœdema of adults, first described by the English writers W. Gull and W. Ord, in 1873, and referred by Hadden to the thyroid in 1882, is usually a rare disease. The morbidity, however, has a way of rising at intervals without any ascertainable reason, as it did in England between 1870 and 1883. Sometimes the reason for the rise is apparent, as in Germany between 1916 and 1921, when food was scarce and when I myself observed a great many cases. Women are much more liable to the condition than men (Heinsheimer reports only ten male cases to one hundred and seven female), and mothers are affected more often than childless women. The onset is usually at or after the menopause, or in men at about forty-five years of age.

Ætiology.—Apart from the cases, rare nowadays, of myxœdema strumipriva due to operation, very few cases have a known ætiology. An inflammation of the thyroid after illnesses and infections, such as typhoid, influenza, erysipelas and dysentery, sometimes progresses to abscess-formation and myxœdema, but the cause is usually obscure. The great preponderance of multiparous women among the reported cases suggests an endocrine factor : the exhaustion of some member of the system, for instance, setting up some kind of reflex strain on the thyroid gland. In this connection, exogenous factors like overstress, worry and under-

nourishment, especially shortage of tryptophane (see p. 19) play an important part. During the years of scarcity the number of myxœdema cases rose tremendously, for the same reason that the number of cases of Graves' disease fell sharply. In some patients the disease is obviously the product of a congenital factor, the " hypothyroid constitution ". Myxœdema patients not infrequently come from families in which there is also goitre or other conditions

Fig. 4.—Myxœdema in a woman of 50. Severe chronic case, untreated. (Author's case.)

resulting from lack of thyroid secretion, and from those in which there is endogenous obesity.

Symptoms.—The *skin* change is obvious and prominent : the hard, almost incompressible œdema of the face, forearms, legs, and later of the trunk, develops gradually and progressively. The face, especially, is grotesquely disfigured by the swollen lids, the thick pendulous folds of the cheeks and the double chin, and water retention is also demonstrable in other tissues. An increase in the fat-deposit is common, but not

invariably present. In addition, the skin is dry, harsh, poor, easily chapped, entirely lacking in sweat or fat, inclined to desquamate, and hyperkeratotic on the palm and soles. The skin is pale grey or golden-yellow and, less often, pigmented ; the mucous membranes are also pale, and pachydermia is often seen as well, especially in the larynx. The *hair* of the

Fig. 5.—Myxœdema in a woman of 50. The same patient after four weeks' treatment with thyroid extract.

head, beard and eyebrows and of the body falls out, sometimes almost completely. The remaining hair does not, however, turn grey, as it does in Graves' disease, but in some patients it changes colour. The teeth often become carious and fall out, but changes in the nails are less common.

The *thyroid* is generally impalpable, less frequently diminished, and wholly or partly indurated. Enlargement

of the gland is very rare. On section it is hard, fibrous and yellowish white, and shows marked increase in the growth of the intra-alveolar connective tissue and atrophy of the parenchyma. Symptoms referable to the other endocrine glands are rare, but anatomically a hyperplasia of the pituitary is sometimes observed, and clinically there may be a diminution in the functioning of the genitals and adrenals.

In the foreground of the clinical picture is the pronounced *general debility* and flaccidity and the general *psychic regression*. Actual paralyses hardly ever occur, and amyostatic or cerebral motor disturbances are very uncommon, but slowness, weakness and lack of energy are betrayed in every movement. They are an accurate reflection of the mental changes, which may be the first part of the picture to develop and which show themselves in a general psychic impoverishment, a blunting of all the higher faculties. Memory, attention, observation, co-ordination, and other functions are progressively impaired. The patient's extreme lassitude, listlessness, and dullness contrast strongly with the abnormal excitability of the Graves' patient. Genuine dementia and frank psychoses are to-day rare, but used to be common; in 1882 the English Medical Commission on myxœdema reported gross mental disorder in 50 per cent of the cases.

All *sensory nerves*, with those of sight, taste, smell, and especially hearing, suffer impairment of function, but there are no other organic neural disturbances. The tendon reflexes are generally weak, and the genital functions are always diminished or entirely arrested.

The *metabolism* is always disordered: the cardinal clinical symptom is the diminution in the gaseous interchange (Magnus-Levy and others); the basal metabolism may be reduced by 60 per cent or more, and in slight and medium-severe cases I found values of – 25 to – 30 per cent.

The following table is made from observations taken, on a spinster of 43, with the Knipping apparatus. It shows the typical disturbance of the gaseous exchange.

Date.	Oxygen Consumption.		Carbon Dioxide Output. Total.	Per Kg.	Total Calories.	Benedict Reading.	Basal Metab.	Treatment.
	Total.	Per Kg.						
1925.							Per cent.	
May 2	145·54	1·9	181·92	2·4	1108	1452	−31	From May 2 to June 19.
June 19	173·58	2·4	182·72	2·5	1267	1442	−14	Thyroid ext.
July 1	162·14	2·2	162·14	2·2	1183	1466	−24	Thyroid reduced.
Sept. 21	155·10	2·1	136·85	1·8	1107	1476	−33	Thyroid stopped.

It is obvious from the table that the gaseous interchange is promptly raised by thyroid extract, but not, of course, to normal; on the contrary, the basal metabolism remains lowered by about 14 per cent, a phenomenon often observed in patients whose thyroidal function seems clinically to be completely compensated. When the thyroid extract was reduced and stopped the basal metabolism promptly sank again to 24 and 33 per cent respectively.

Nevertheless, the specific dynamic action of protein on the basal metabolic rate remains unaltered. As for the parts played by the individual food-stuffs, their oxidation level is lowered to about the same extent for all with the exception of sugar, for which there is an increase in tolerance, as is shown by the absence of rise in blood-sugar level on the administration of dextrose and the injection of adrenalin. The protein metabolism is greatly reduced, and protein should be pushed in the diet in spite of the reduction in the total intake. Even on a very restricted diet the nitrogen-equilibrium remains unimpaired. The low protein metabolism is reflected in the raised protein-concentration and increased viscosity of the blood-serum (G. Deusch). That the water economy is badly disordered is shown by the water-retention in untreated cases and the immediate flushing-away of the œdema that takes place when thyroid extract is given. Oliguria persists. Eppinger found that thyroid had a marked influence on the excretion of salt and water, and that its diuretic properties were not due to any direct effect on the kidneys but to a mobilization of salt and water in the tissues.

In view of the reduction in metabolism it is noteworthy that patients on ordinary or even meagre diet grow fat, or at any rate appear to. There are incomplete cases in whom the tendency to obesity—thyrogenic obesity—is the most conspicuous symptom ; apart from these, untreated patients grow thin and cachectic after some years of illness.

The **course** always exhibits certain typical features. The pulse is nearly always retarded and the blood-pressure often, though not always, lowered. The uniform dilatation and

FIG. 6.—Myxœdema adequately compensated with thyroid extract. A woman of 65 ; her appearance is remarkably youthful, and her hair shows no sign of greyness. (Author's case.)

weak, sluggish action of the heart, described by H. Zondek and Maas, were apparent in my cases, but I cannot confirm their report of the constant appearance of certain changes in the electrocardiogram (absence of the auricular wave and final oscillations, and presence of oscillations towards the end of the ventricular extrasystolic waves).

The sluggishness of the vasomotor reactions as shown in the plethysmogram is also very apparent clinically, and contrasts with the over-excitability that I found with the plethysmogram in Graves' disease. Independent of the

vasomotor disturbance, though related to it, is the tendency to acrocyanotic pallor, especially of the face.

The blood does not usually undergo any gross changes ; secondary anæmia is common among bad cases, but alterations like those in pernicious anæmia are unknown. There is always an absolute or relative lymphocytosis. In contrast to Graves' disease, the viscosity and protein-concentration of the serum are greatly increased, a change which corre-

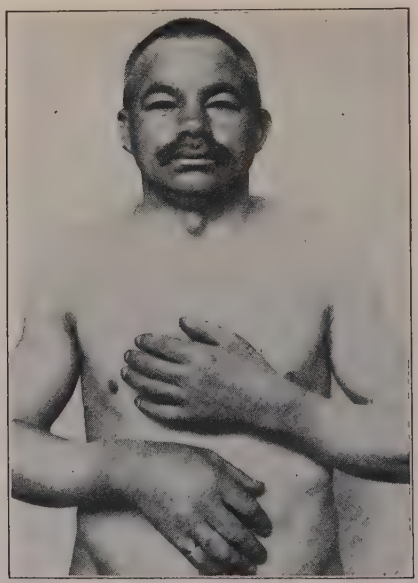


Fig. 7.—Myxœdema in a man of 42. (Author's case.)

sponds to the diminished protein metabolism, and there is a reduction in the coagulation time, together with a drop in the iodine content of the blood.

The respiratory organs are not, as a rule, especially involved. On careful examination and with recording apparatus, a slight shallowness and slowness of breathing can be detected.

Of abdominal symptoms, constipation is the most prominent ; it is quite constant and proportioned to the severity of the disease, and is in my opinion one of the

cardinal symptoms. On X-ray examination a marked atonia is evident; the haustra in the colon are shallow and broad, and there is usually ptosis of the transverse colon, and hypotonic movement of the small intestine and stomach (G. Deusch). The gastric secretion and acidity are generally diminished, and the appetite is poor.

Many of the patients develop an umbilical hernia. The liver and spleen are seldom altered. The bones and joints are usually intact; rheumatic pains and gross joint changes are rare. Sometimes, especially in elderly women, there is osteoporosis or osteomalacia.

The **pathogenesis** is quite clear, for extirpation of the thyroid gland produces the same clinical picture as its spontaneous atrophy. The cause of all the symptoms is the impoverishment of the organism in thyroxin, and especially the loss of the stimulating effect of the thyroid hormone on the vegetative nervous system, the other endocrine apparatus, and the metabolism.

The **prognosis** depends entirely on the treatment. If this is appropriate, the prognosis is good; if not, the illness may progress for years and end fatally.

Treatment consists in replacing the missing thyroxin, and all other measures are merely accessory. Kowitz established that in moderately severe cases, 0·1 grm. of thyroidin[1] twice a day restored the basal metabolism from −35 per cent to normal in a fortnight, and so we ourselves do not use larger doses. Thyroidin sicc. (Merck) in tablet form, 0·1 grm. twice or thrice daily, should be exhibited for a fortnight or three weeks at first, and the weight and, where possible, the metabolism, should be checked regularly. Later it is usually possible to reduce the dose. It is nearly always necessary to go on giving 0·1 grm. of thyroidin once or twice a day for several months, and to some patients for a year with intervals of rest. On the appearance of the symptoms of hyperthyroidism (tachycardia, sweating, and so forth) the

[1] Translator's Note.—The author refers to thyroid extract throughout as "thyroidin", the dry preparation marketed by the firm of Merck. Except where exact doses are given the term "thyroid extract" has been substituted in the translation.

exhibition of the drug should be discontinued. The diet should be relatively rich in protein ; in other respects it may be arranged to suit the palate. A certain amount of rest and relaxation, and, usually, a period of release from the ordinary occupation, are necessary and natural. Under this regime all the symptoms almost invariably disappear within a few weeks. The patients, subjectively and objectively, are " born anew ", and continue in that happy state if they take thyroid long enough and do not take too much.

Incomplete Forms of Myxœdema

The kind of case especially described by Hertoghe as " chronic benign hypothyroidism " is not extraordinarily rare, but calls for an exact definition in order to avoid an arbitrary and excessive use of the term. It was known long before the Great War, but I remarked a relative increase during the years of scarcity and a subsidence of the wave when conditions became normal again. These forms, like the complete form, are commonest among women, and I have seen them comparatively often in the childless.

Symptoms.—Myxœdema may be said to be incomplete when the gross pachydermatous skin changes are lacking. The soft œdemas are impermanent and often fluctuating ; a chlorotic or thymo-lymphatic habitus is fairly common. Obesity of thyroidal origin is relatively frequent, but normal fat deposit is seen as well. Subjective disturbances, such as languor, fatigue, loss of energy, psychic regression, sensations of chill and abnormal sleepiness, are prominent. Sweating is nearly always reduced and constipation is invariably present. Very often scanty menstruation or amenorrhœa sets in. Cardiac disturbances are not a constant feature, but bradycardia and hypotension are often observed. H. Zondek has also found dilatation and certain alterations in the electrocardiogram (see above, p. 27) ; he goes so far as to describe these as the cardinal signs of hypothyroidism.

Relatively frequent are pustular, ulcerative or eczematous dermatoses, onychia, paronychia, loss of the nails

and extensive loss of hair, painless loss of teeth and other trophic disorders.

I have selected the following examples from my own experience :

i. Transient œdema of the face and hands, psychic depression, gastric achylia, constipation and a considerable gain in weight.
ii. Obesity, menopause, psychic regression, constipation and chronic, obstinate, pustular, ulcerative dermatitis.
iii. Loss of psychic vigour, amenorrhœa, " incurable " generalized eczema, constipation.
iv. Total alopecia, fatigue, scanty menstruation.
v. Acute abdominal obesity recurring every winter, associated with relapsing constipation and sluggishness.

The **diagnosis** should be made with great care, but it is not a difficult one. It is clinched in all cases by the immediate improvement under thyroid, which test *ex juvantibus* is recommended unconditionally as a diagnostic measure. Metabolic tests, especially that of the basal metabolism, should always be performed. The basal metabolic rate is lowered in most hypothyroid cases, but not in patients who happen by coincidence to have a psychoneurosis together with obesity. A few rare cases of chronic hypothyroidism, however, have a normal basal metabolic rate.

To the incomplete forms of hypothyroidism also belong those cases in both sexes, for the most part elderly, described by Eppinger as suffering from forms of chronic cardiac insufficiency and nephrosis accompanied by œdema unduly severe in proportion to the relatively minor heart trouble. He saw them get rid of their dropsy rapidly under thyroid extract. Metabolic tests have not yet definitely proved the thyroidal origin of these cases.

The cause of chronic benign hypothyroidism lies, on the one hand, in the constitution, and on the other, in certain exogenous factors, of which the most important seems to me to be the alimentary one I have already mentioned, the scarcity of tryptophane in the diet. Constitutionally, patients of this kind usually show " hypothyroid stigmata " ;

many, again, come under the heading of congenital thyroidal hypoplasia.

Since **treatment** with thyroid extract is almost invariably successful, the **prognosis** is good.

Cachexia Strumipriva

This disease, which nowadays has become very rare, was first recognized by Th. Kocher. It used formerly to be commoner, especially, as is natural, in countries much troubled with goitre. Soon after—and sometimes a few weeks or months, and even more than a year after— thyroidectomy, usually a total one, patients sicken with quite general symptoms : severe exhaustion of the limbs, lack of energy, sensations of chill, insufficient warmth and a psychical decline much like that of spontaneous myxœdema, which is often fairly rapid but which may come on slowly. The mental disturbance is generally much more severe than in the spontaneous form. There appear at the same time typical myxœdematous changes in the skin, nails and hair, but only occasionally obesity. In addition, the genital functions deteriorate, and the patient suffers from amenorrhœa or impotence.

The younger the patient the more acute are the symptoms. In children the bone-development suffers severely and the epiphyses do not unite ; the growth is arrested, and the clinical picture becomes one of hypothyroidal dwarfism. The genital development, including that of the secondary sexual characteristics, remains infantile, and the psychic development sometimes, by no means always, follows suit.

Metabolism, blood, circulation and vegetative system show the same typical changes as in the spontaneous forms.

An important and highly alarming symptom occurred in patients whose *parathyroids* were excised with the thyroid : they developed an extremely severe tetany with violent convulsions, and sometimes tetanic epilepsy as well (the symptomatology is described under its own heading). Not all patients, however, suffer from tetany after total removal ;

probably those that escape have an ectopic parathyroid which has been overlooked, and continues to function vicariously. Such patients, moreover, have been observed to suffer only from a mild myxœdema or to recover spontaneously after showing severe symptoms. Sometimes this occurrence has been explained by the subsequent demonstrable swelling-up and vicarious functioning of a small piece of gland that has escaped removal at operation.

Typical myxœdema has also been noted after *partial thyroidectomy* : this is caused by post-operative atrophy of the remaining portion of the gland. I have seen two such cases in the same half-year, and they are probably more common than is generally believed.

The course of *total thyroidectomy* cases is usually stormy, distressing and serious, and if treatment is incomplete the **prognosis** is bad. In former days deaths were not uncommon.

Treatment by thyroid extract, graduated according to the severity and basal metabolism, has achieved excellent results in our clinic. It should be combined with measures directed against the tetany ; the best of these, in the critical state in which most patients find themselves, is the intravenous injection of calcium. We use the preparation known as " Afenil ".

X-ray Myxœdema

Under " X-ray myxœdema " we class, by analogy with cachexia strumipriva, those patients who develop myxœdema after irradiation of the thyroid, usually for Graves' disease. They are generally, like two I have seen, relatively mild cases of hypothyroidism, who show of course all the metabolic symptoms but none of the severe asthenia, mental hebetude or cachexia, that the surgical cases exhibit. As far as I know, they never suffer from tetany.

Occasionally a case of Graves' disease will go over spontaneously to myxœdema, especially in Graves' patients with isolated hypothyroidal symptoms. My cases of X-ray myx-

œdema, for instance, were women who had had Graves' disease with a predisposition to obesity, a relatively moderate rise of basal metabolic rate, a placid temperament, and other previous marks of vagotonia. These occurrences show the necessity for extreme care in treating Graves' patients with constitutional features of this kind by X-ray.

Hypothyroidism in Children

These forms, which have been described—not altogether happily—as " sporadic cretinism ", can be classified, after the example of Pincles and others, as

i. Congenital thyro-aplasia.
ii. Acquired infantile myxœdema.

Neither form is by any means confined to districts which abound in goitre and cretinism.

Congenital Thyro-aplasia

This is a rare disease, but much more frequent in female children than in male. Opinions are divided on how far it is hereditary. Often its incidence is sporadic, but it is apt to occur in more than one member of a family. A neuropathic constitution, tuberculosis, syphilis, and consanguinity of the parents appear to play a certain part.

Course and Symptoms.—The children have apparently been normal at birth, and their physiological and mental development has appeared, at any rate to the parent, to proceed normally for the first few months. After six months or a year, however, the typical marked disorders set in, and development is arrested. Progress in standing erect and in the production of speech and sounds ceases. Gradually there develops the picture of the myxœdematous cretin ; the skin becomes thick, spongy and—usually—pale, the lips swollen, the eyes slit-like and mongoloid from the swelling of the lids, and the cheeks fat, while double chin and a fatty swelling of the nape make their appearance. The arms, legs and trunk become gross, and the belly becomes misshapen ; umbilical hernia often develops. No further growth in

height takes place, and dwarfing always results. Patients of ten are only of the size of a normal child of three or four, and those of fourteen may only measure 3 ft. 8 ins. in height. The bone growth is stunted; the fontanelles remain open abnormally long, and the epiphyseal lines remain cartilaginous after the twentieth year. Gross bony changes and deformities are often absent, unless rickets is associated, which is seldom seen. The plumpness of the extremities usually depends upon the growth of the soft parts, and more especially upon the extreme obesity. The skin is dry, the extremities often cool and cyanotic. The hair is coarse, discoloured and often scanty. The sexual development is arrested at the stage of early infancy, and the secondary characteristics never appear. The metabolism is generally as retarded as in adult myxœdema, especially the respiratory basal metabolism, which is nearly always markedly diminished. The normal basal metabolic rate of children has of course been observed to be higher than that of adults, and so its diminution in hypothyroidal children is relatively slight. The same disorders of water and chlorine metabolism, and the same secondary anæmic changes of the blood and low viscosity and protein concentration of the blood-serum, are observed as in adults. There is nearly always severe constipation.

Fig. 8.—Congenital thyroaplasia; severe case in a boy of 4¾. Height 2 ft. 4 ins. Toothless; open fontanelle; extreme atrophy of the skull and extremities; herniated navel. (From Siegert.)

The thyroid gland is quite impalpable, and goitre is never found in unmixed cases.

In complete cases all these cretinoid changes are highly developed, including those of the mentality ; the psychic activities are usually restricted to the necessities of organic existence. The patients never learn to speak, remain dirty, and often lack any sense of contact with their environment.

Fig. 9.—Moderately severe congenital case. $3\frac{1}{2}$ years. Height 2 ft. $4\frac{2}{5}$ ins. Typical case. Treated as rickets for two years until suspicion of myxœdema was confirmed from another source. Two incisor teeth. Grew $9\frac{3}{5}$ ins. in eighteen months. Intellectual development and ability to stand remain unsatisfactory. Appearance now normal. (From Siegert.)

Naturally there are also cases (with severe bodily disease) which only show a slight degree of amentia.

The life of these beings—without treatment—is short. Most of them die as children, but some live, in spite of complete imbecility and great frailty, to over thirty.

The *cause* of the illness has been found anatomically to lie in a congenital total absence of thyroid gland ; occasion-

ally microscopic " rests " are demonstrable (Erdheim). This explains the extreme severity of the symptoms. That the myxœdematous symptoms are first manifested relatively late, after apparently remaining latent for some months or even more than a year from birth, may well be due to the supply to the child from the mother's blood, and later from the milk, of enough thyroxin to make good the deficiency. The reason why children without thyroids do not all die speedily (like some adults who lose it at operation) may be that their parathyroids attain normal growth and have a compensatory effect. It is a fact that thyro-aplastic children are as a rule free from tetany.

Fig. 10.—Congenital case of medium severity, æt. 12 years. Height 2 ft. 2 ins. (Treated from the age of six with quite inadequate doses: 0·5 to 0·1 grm. per day.) Typical relapse. He is now 30 and somewhat resembles children of 9-10 years of age. (From Siegert.)

This naturally does not apply to those few children who develop cachexia strumipriva after operation. They evolve the severe complete type of myxœdema with physical and psychical changes that recall the grotesque forms of endemic cretinism; their growth and the development of their bones and genital system remain as they were at the time of the operation, but most of them fall ill with tetany. If not treated, children with this syndrome probably all die.

Congenital Infantile Hypothyroidism (Thyrohypoplasia congenita)

As in adults, so in children, there are cases of chronic, relatively or absolutely benign hypothyroidism, some of which indeed are clinically, and also sometimes anatomically,

classifiable as congenital dysplasia. How common they are it is difficult to say, since they often pass unrecognized by their friends and the doctor (who may not have the specialist's interest). They do not, however, seem to be very rare ; probably many of them have no hereditary taint of goitre or cretinism.

Symptoms and Course.—They are born apparently normal, but their development appears slow in many ways without the defect being very conspicuous. Sometimes the dysplasia is first discovered by a school medical officer after the sixth year. They grow well, but much more slowly than other children of their age. This *shortness of stature*, which occurs even in the children of tall families, is the characteristic symptom. The bone growth is correspondingly very much delayed, especially that of the centres of ossification in the epiphyses, which remain permanently separated (Wieland).

Apart from this there are more or less marked *skin changes*, such as dryness, swelling, cold, cyanosis, and so forth. The thyroid is not palpable. The complexion is pasty. Secondary anæmia is common, also lymphocytosis and esinophilia. The temperament is "good-natured, passive, shy and reserved" (Wieland), but grosser psychic disorder, including marked impairment of the intelligence, may be lacking. A certain subnormality of talent is perceptible in school at almost all times. The voice is usually low, harsh, and rather hoarse and deep.

There seem to be no satisfactory data extant about the *metabolism*. It is, however, permissible to assume, by analogy from cases of incomplete acquired myxœdema in children, that in congenital cases also there is a diminution in the respiratory basal metabolism, though probably not a very great one. Wieland has declared that tests show heightened sensitivity to atropine and lowered sensitivity to adrenalin. Constipation is the rule.

The *sexual development* is more or less retarded in both sexes ; this applies especially to the secondary sexual characteristics of the male. The men have practically no facial hair.

It is most important to note here that (as has been mentioned already) many cases pass from this picture of benign congenital hypothyrosis to that of the chronic benign hypothyroidism of adults described by Hertoghe. I refer to patients who have passed from youth up as possessing hypothyroidal " constitutions " or " temperaments " ; those relatively small, sturdy, rather pasty, silent, modest persons with weak growth of hair and beard, prone to tire easily and very sensitive to cold, who doubtless seem to us (and to themselves) not to suffer from manifest illness but simply to have some constitutional abnormality. The large majority of such cases without doubt belong to the class of thyrohypoplasia congenita, and make up the mildest groups. It may be observed that such cases of slight hormone imbalance, when subjected to influences from the outside, such as underfeeding, infection, and fatigue, fall ill with Hertoghe's syndrome (p. 30) of manifest, though often incomplete progressive hypothyrosis, generally in early adult life.

At the other end of this chain stand serious cases of infantile congenital hypothyrosis which approach in their symptoms the total thyro-aplasia, but nevertheless retain a passable degree of social and intellectual competence—finish their schooling, for instance—in spite of apparently bad physical disfigurement and complete infantilism. The metabolic and blood changes are naturally more constant and pronounced in these than in the milder forms.

It is important to avoid the error of attributing diagnostic significance to the morphological blood-picture in all these cases, but the gas interchange (if the technique is correct and results are considered critically) and the diminution of serum concentration have the greatest diagnostic value.

Acquired Infantile Myxœdema

Pincles and I agree that such a form exists, but it is very rare. Most cases of myxœdema in children have doubtless a hereditary basis. It is permissible to diagnose this form only when it is certain that the child did not have a hypothyroidal constitution before it became ill. These patients

are definitely normal at birth and develop normally until the illness, which usually begins between the fifth and twelfth years, often—and this is pathognomonic—after an infection, such as measles, erysipelas, typhoid or syphilis. Sometimes, however, there is no exciting cause, and in these cases it is especially important not to give a diagnosis of acquired myxœdema without very careful consideration. The myxœdematous symptoms that follow the outbreak are, as far as the skin, metabolism, blood and mental picture are concerned, those of congenital hypo- and athyrosis. The bone growth shows the typical interruption or delay from the date of the onset. Therefore, when this occurs relatively late, say after the tenth year, the picture is different and less severe then in athyrosis, and there is less interference with the growth in stature and the sexual development; but even so, this form is likely to lead, like the other, to sexual infantilism.

Fig. 11.—Infantile myxœdema with dwarfism in a boy of 9. (Author's case.)

On the psychic side there is a large possible variety of symptoms, from a simple and hardly perceptible arrest of psychic development, which may not hinder attendance at school or an easy occupation, down to the lowest grades of cretinous idiocy.

The thyroid is, as in the myxœdema of adults, usually impalpable, and shows anatomically the same atrophic and sclerotic changes. Others as well as myself have sometimes seen these patients develop tetany and tetanic epilepsy.

It must also be noted that, while in cases of this class all symptoms of physical and psychic defect are usually mild, a spontaneous change to severity is not uncommon. The

pachydermia is sometimes only slight ; it may, for example, be confined to the face. This is probably the form exhibited by a certain number of cases of the chronic benign hypothyroidism of adults (p. 30).

Treatment of both the congenital and acquired hypo- and athyroses in children, as in adults, consists in the exhibition of thyroid extract, of which the dose must be proportioned to the age. For children of two years the common dose is 0·025 grm. of thyroidin sicc. (Merck) once a day for a few days, then twice and later three times daily. The metabolism, weight and general condition will soon determine what dose will ensure full compensation. Children of ten and over may be given, like adults, 0·1 grm. twice a day. I have observed that, on the whole, children even under five are relatively tolerant of thyroid, and can take fairly large doses without toxic symptoms and with good results. The basic maxim of all thyroid treatment holds good here as well : increase and decrease the dose experimentally, until the right level is found, and continue for months, and if necessary, for years. In treating young children and babies, especially those with spasmophilia, it is particularly necessary to keep a careful watch on the diet, especially the vitamin intake, and under some circumstances to order calcium or sal-ammoniac (see Tetany). The rule of providing an adequate supply of meat-

Fig. 12. —X-ray picture of the hand of a boy of 9 with infantile myxœdema. Extraordinary delay in ossification : there are only three centres of ossification in the carpal bones. (Author's case.)

protein holds good also for children of school and pre-school age.

Course and **prognosis** are, on the whole, very good if thyroid extract is given early in correct doses and continued for a year or more. It often brings about—especially in congenital and acquired hypothyroses—a complete return

Fig. 13.—X-ray picture of the hand of a normal boy of 9. (Author's case.)

of fallen hair and practically normal bodily dimensions, genital development and physical and working capacity. In bad cases of aplasia the physician often has to be content with slight, sometimes feeble improvements, very far short of the typical "rebirth" seen in adult patients. Many cases of thyro-aplasia, even on thyroid, never attain to physical and psychic perfection, and not a few succumb

early to intercurrent disease. Nevertheless, even in such relatively refractory cases the increasingly energetic administration of thyroid extract is obviously most important. The error of giving it up altogether for slight disorders and replacing it with various " tonic " treatments, such as brine baths, cannot be too strongly condemned.

Endemic Cretinism

Numerically this disease is by far the commonest of the infantile hypothyroses. It is essentially endemic, as its name implies, in districts where goitre is rife ; above all, in the Alpine countries of Central Europe. Infantile cretinism is especially common in families in which some of the members suffer from goitre, cretinism or cretinoid degeneration. The frequency of this form of dystrophia is difficult to estimate, as numerous slight " cretinoid " conditions tend to be included with cases of the real disease. Nevertheless, it is very great. In Styria, for instance, the number of cretins per hundred thousand of population is reckoned to be a thousand. Male children are more often affected than female. In places where goitre is scarce, like the German coast, it is extremely rare. It often appears as early as the first year, manifesting itself in cretinous disfigurement of body and face, especially in a very marked arrest of growth. Dwarfism is the rule, and only in cases of relatively late onset does the height reach 5 ft.

Course and Symptoms.—In addition to the *arrest of skeletal development*, already described, changes are seen, akin to those of rickets, such as curvatures and crookedness of the long bones and narrowness and flattening of the pelvis. The skull often acquires an extremely low platycephalic shape, with premature fusion of the sutures and a peculiar shortening of the basis cranii due to early fusion of the three basal bones (Ewald). Saddle-nose is also part of the picture.

Next to the dwarfism the most typical manifestation is the shape of the face ; the low, retreating brow, the saddle nose, the prominent mongoloid cheek-bones and oblique

slit-eyes, the puffed-out lips and large tongue, the broad, low under-jaw with very poor dentition, and the short neck with its swollen sides, all distinguish the cretin. The expression of this—in most cases—excessively repulsive face reflects the child's more or less complete amentia.

The *skin* is in part typically myxœdematous and in part

Fig. 14.—Cretinism with goitre. (After von Bruns.)

of the usual thickness, but flaccid and grossly wrinkled "as though it were too large", and sometimes even senile. There is generally secondary anæmia, and not infrequently abnormal pigmentation. The mucosæ are sometimes also thickened, the hair is sparse, bristly and discoloured, and the nails are often badly formed. The trunk is squat, the breast flat, the legs short, bandy and plump, and their

muscles exceedingly weak. Many patients are unable to walk, and many never progress unassisted beyond a crawl. A pendulous belly and umbilical hernia complete the grotesque picture.

The *thyroid*, which in adult cretins is so often subject to goitrous change, is said by Wieland to be not infrequently enlarged in children under 14; only occasionally are they found on palpation to possess a normal or nodular and somewhat enlarged thyroid. In older cretins the nodular and often very large thyroid is common, though its incidence varies very much in different districts; Styrian patients are rarely goitrous, but the Swiss nearly always are. Obesity is only present in some cretins, and is often absent in severe and elderly cases.

Fig. 15.—41-year old cretin. (After H. Zondek.)

The *nervous disturbances* are entirely governed by the *psychic*, which are present in all cases. The intelligence of full cretins is often below that of animals: it is almost impossible to gain their attention; they cannot speak, they have no perception, they are unclean and often unruly, and most unpromising objects of attention. All grades of idiocy and feeble-mindedness are seen. In slight cases or so-called "cretinoid" individuals the psychic disorder manifests itself (as in cases of slight hypothyrosis) merely in a certain mental numbness and poverty which may allow them to make a living even at so-called brain-work if, as sometimes happens, the attention and memory are good. Difficulty of hearing, deaf-mutism and disorders of smell and taste,

are not rare. The sexual development usually remains at an infantile level, and the secondary characteristics fail to appear. In slight cases the development may be more or less complete, though it is generally very late.

The protein, chlorine and water metabolism is slow and diminished, as in myxœdema. The gaseous interchange, especially the basal metabolic rate, is similarly reduced in pure cretinism. This sluggishness, however, may be changed to an increase if (as occasionally happens) thyrotoxic symptoms are mingled with those of goitre and cretinism (H. Zondek). According to Kraus and others, these cases, in whom the Graves' syndrome is never complete, belong to the relatively mild forms of cretinism.

The **ætiology** and **pathogenesis** are hotly contested; even the rôle of the thyroid is vigorously challenged. The cause is probably based on factors of germ plasm and environment, which also evoke other forms of endemic dystrophy. A lack of iodine in the food—especially in the water—climate and heredity probably play a part in cretinism and goitre alike. It must be noted that endemic cretinism differs essentially from other forms of infantile hypothyrosis. Pincles says that total disappearance of glands once grown, or aplasia, is never seen in endemic cretinism. Recently there has been an increase in the number of authors who deny to goitre any causal significance whatever; who speak, not of goitre and cretinism, but of "endemic dystrophy" and hold that the stock of the patient is the preponderating factor. They point, for instance, to the similarity of cretins to Mongols or even to neolithic pygmies. I share the opinion of those who believe that these "anti-goitrous" theories are exceedingly wide of the mark.

The results of **treatment** seem to support the opponents of thyroid therapy, for there is no doubt that only a small proportion of cases of endemic cretinism benefit from thyroid extract. It is frequently useless, and sometimes very harmful. This is not surprising when it is remembered that cretins may show hyperthyroidal symptoms as well. The metabolism, especially the basal metabolic rate, should be taken as the indication, and thyroid should

only be given systematically if this is substantially below normal. Wagner von Jauregg and Magnus-Levy have, in fact, obtained good and far-reaching results with thyroid extract in cases where the metabolism was lowered and myxœdema preponderated.

Many authorities believe that minimal doses of iodine reduce the incidence both of cretinism and of goitre, but it is very improbable that small quantities of iodine can influence cretinism once it is manifest.

The **prognosis** is much more obscure than that of the pure hypothyroses and athyroses. In cases suitable for thyroid it may be fair, but it is never good; in others the prognosis, as far as health is concerned, is generally bad. The miserable creatures often have a comparatively long life, many completing sixty or even seventy years.

Mongoloid Degeneration

Under this heading we class, with Weygandt, certain forms of mental deficiency and allied conditions which are presumably related in some way to endocrine disturbances, but which cannot be shown definitely to depend on them. Their relation to endemic cretinism and hypothyroses as a whole has been affirmed, but is by no means proved or even likely.

Symptoms.—Children and adults with innate (or more rarely with acquired) mental defect of various grades have a strikingly *Mongolian cast of face*, with a flat nose, broad cheek-bones, slit eyes placed abnormally far apart, and epicanthus. The face is somewhat bloated and the mouth hangs open; the tongue is often enlarged and deeply wrinkled or "scrotal". The skull is hyperbrachycephalic and has an abnormally small circumference. The dimensions are usually two to six inches below normal, owing to the arrest of skeletal development, which recalls that of the cretin. Dentition is delayed and irregular. Joints, muscles, ligaments and other structures show abnormal lack of tone and flexibility.

The *skin* is pasty, turgid and often dry, and there is a tendency to acne, blepharitis, eczema and similar ailments.

The *sexual development*, including that of the secondary characteristics, is arrested, as it is in certain cretins. Gross congenital malformations and stigmata of degeneration are common ; these may include congenital heart defects, strabismus, nystagmus, umbilical hernia, malformations of the nose and ears, and the like. Vasomotor changes, especially acrocyanosis and abnormal coldness of the extremities, are often seen.

The *mental picture* shows various grades of idiocy : some children learn a few words only or none at all, are quite ineducable and simply vegetate ; others possess rudimentary talents, such as mimicry and buffoonery (Weygandt), and are able to master very simple handicrafts. Many are relatively docile and good-natured, and violent patients are in the minority.

Little seems to be known about the *metabolism* ; I found in one case a normal basal metabolic rate and serum-concentration and a normal water and chlorine metabolism. Morphologically the blood was quite normal. Kafka found anæmia, neutrophilia and leucocytosis with eosinophilia, together with a rise in the sedimentation rate.

Anatomically the brain is abnormally small and light, and is subject to various kinds of dysplasia ; for example, the structure of the cortical cells is of an embryonic type, and the tangential fibres are poorly developed (Weygandt). Hydrocephalus and meningitic changes have been described. Clinically, epilepsy and all kinds of ataxic and choreiform motor disorders have been observed.

Course.—The first symptoms are generally observed in early childhood. As babies, mental defectives are abnormally quiet and immobile. Often, however, psychical and physical defects do not become obvious until the child learns to speak or goes to school. The capacity of both mind and body to develop varies, but is as a rule very slight. The expectation of life, on account of the increased liability to infectious disease, especially tuberculosis, is much curtailed, and patients only rarely live beyond the twentieth year.

It appears that certain varieties of mongolism, like the " Malayan " or " Eskimo " types of Heller, show milder

symptoms, have a greater tendency to compensation, and take a longer time to mature.

The **ætiology** and **pathogenesis** are not yet clear. Mongoloids have generally been observed to be the offspring of very old parents or those related by blood, or to be the last of a very large family. The idea of a "pre-formed degeneration" in the germ-plasm has been accepted and has led to an "exhaustion" theory of the cause (Weygandt). Of exogenous factors syphilis of the parents, and more especially of the grandparents, is probably important (Clemenz).

The rôle of the endocrine system has not yet been made clear. Kafka, experimenting on the lines of Abderhalden, found on some occasions a degeneration of the cerebral cortex and pituitary.

The results of **treatment** with organic products, especially thyroid, do not substantially support an endocrine ætiology. In my own experience, as well as in that of others, these results are very insignificant and confined to a certain physical improvement. The mental defect seems hardly to be affected. To give the best care and to make the most of what educational possibilities there are, it is necessary to send the patient to an institution.

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DISORDERS OF THE PARATHYROIDS

Anatomy and Physiology.—The parathyroid glands, which were discovered by Sandström and named the "epithelial bodies", and recognized by A. Kohn and Vasalle and Generali as anatomically and physiologically independent organs, consist of two pairs of soft, reddish bodies, each about the size of a lentil, which in man lie behind the lateral lobes of the thyroid. Their position and number may, however, vary. Like the thyroid, they are very vascular. Histologically they are made up of large polygonal mother-cells and smaller oxyphil cells (Welsh), and contain glycogen and colloid.

Their function was first recognized by the effect of removing them along with the thyroid; patients and animals who lost them developed both myxœdema and tetany. It was further established that animals that had lost their parathyroids and patients suffering from tetany both had an abnormally low blood-calcium, and that all tetanic symptoms were removed when calcium was exhibited (McCallum and Vögtlin). Recently Collip has prepared a very effective extract from bovine parathyroid, which prevents tetany in parathyroidectomized animals when administered with calcium. It is therefore justifiable to infer that the regulation of the calcium content of the blood and tissues is an important function of the parathyroid.

Adult Tetany

Tetany, first described by Steinheim and Corvisart, is a spasmodic ailment which is fairly uncommon in adults, and is due to many different causes and has very uniform symptoms.

(1) It is relatively frequent among workers in certain trades, such as cobblers, tailors, turners and locksmiths, and the morbidity is confined almost entirely to certain localities.

In Austria and Hungary, especially the large towns; in Baden, Hesse and the whole of South Germany it is fairly common. In North Germany it is very rare. The incidence varies with the season, and is high from January to April.

(2) A second group of conditions in which it is common is gastric diseases, especially benign pyloric stenosis, ileus and severe bowel infections and helminthiasis.

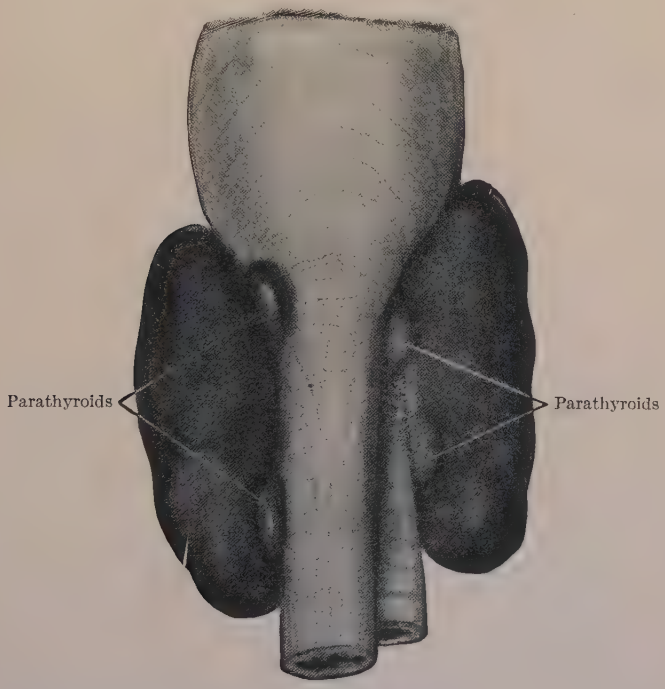


Fig. 16.—Human thyroid and parathyroid; posterior view. (From Zuckerkandl.)

(3) It occurs during pregnancy and confinement, especially between the sixth and eighth months. Like gastric tetany, this form is severe.

(4) It is encountered in many intoxications; for example, in poisoning by ergot, phosphorus, ether, morphine, novocain, etc. Sometimes tuberculin produces tetany.

(5) Very occasionally, tetany appears at the height or

during the incubation of certain infections, such as typhus, influenza, Vincent's angina, malaria and polyarthritis. It generally runs a mild and transient course.

(6) Very significant, but to-day very rare, is the tetany caused by the removal of the parathyroids with the thyroid.

(7) Prolonged and too frequent breathing (hyperpnœa) may lead to tetanic spasms.

The **symptoms** of these forms of tetany, so various in their causation, are very similar. In the foreground is the tonic "tetanic" *spasm*. After the onset of paræsthesiæ—pains, tingling and the like in the hands and feet—there suddenly sets in an intensive tonic spasm, especially in the flexors and adductors of the arms and legs, and in the hands and calves (carpopedal spasm). The attitude of the hands becomes claw-like or obstetrical, and that of the feet equine ; the muscles of the elbows, shoulders, knees and hips are often involved, but those of the trunk and neck less commonly. Occasionally the spasm attacks the muscles of the tongue, face and eyes, causing blepharospasm and spasmodic strabismus. In adults cramps sometimes occur in the glottis, and very rarely the diaphragm is affected as well. It is very probable that in adults internal organs innervated by the vegetative system are also involved in the tetany. It has been observed in the stomach (pylorospasm, gastrospasm), in the bronchi (broncho-tetany, a form of asthma), and even in the bladder.

The cramp of the extremities is nearly always symmetrical, and only very rarely has a pure unilateral tetany been recorded. The duration of the attack varies considerably ; it may last only a few minutes or it may go on for hours or even days (status tetanicus). Certain chronic tetanies have a peak of moderate duration in the late winter, lasting about a week. The intensity of the spasms varies as well. In more acute cases they are often very severe and distressing. Mechanical and psychical stimuli, such as overstrain and warm applications, will often precipitate an attack.

Sometimes the sensory symptoms of the aura predominate overwhelmingly and the succeeding spasm is relatively mild. Occasionally they may even replace the motor spasm

altogether. This form is known as "sensory tetany". Analogous "tetanic equivalents" are sometimes noted in the form of paroxysmal disorders of smell, taste and sight, and of the vestibule. The physical symptoms of the greatest importance for diagnosis are those known as the *stigmata of nervous hypersensitivity*. The most constant of these stigmata is the abnormal sensitivity of the motor nerves—of the face, for example—to mechanical stimulation (the facial phenomenon of Chvostek, senior). Only its higher grades are pathognomonic for tetany. The other motor nerves, such as the brachial plexus and the ulnar and median nerves, also exhibit this sensitivity to percussion.

The motor nerves are also over-sensitive to electrical, especially galvanic stimuli. In fact, Erb's sign, which consists in a heightened (and altered) sensitivity to a galvanic stimulus, is of all signs the most pathognomonic of tetany.

In a positive Erb reaction the cathodal-closing contraction occurs abnormally early; on the right mental branch of the facial nerve it occurs at 0·2-0·3 milliampères, and the anodal-opening and anodal-closing contractions also come early. Sometimes there is tetany on either the anodal or cathodal closing.

Decidedly less constant is Trousseau's sign: cramp in the hand after prolonged compression of the nerves in the bicipital sulcus. H. Schlesinger has described a similar sign in the leg, after abduction of the leg with the knee extended. Still less reliable is hypersensitivity of the sensory nerves (J. Hoffmann), *e.g.* of the acoustic, to mechanical and galvanic stimulation (Chvostek, junior). The vestibule also seems occasionally to be sensitive. Unless the signs of Erb and Chvostek are both present, a diagnosis of genuine tetany should not be made.

Other physical symptoms are sometimes present and sometimes not. Many, like the swollen "tetanic face", falling hair and nail changes, may well indicate an associated hypothyrosis; others, like thinning of the skin, sweats and marked emaciation, may show a disturbance of thyroid function. The most important trophic phenomenon is *cataract*; in young patients this is more usually nuclear,

with or without cortical changes, and in the elderly it is more often cortical. These forms of cataract have also been evoked experimentally in parathyroidectomized rats—a further proof of their connection with tetany (Erdheim).

In addition, many *disturbances of the vegetative nervous system* have been observed, such as vasomotor, secretory and trophic anomalies of the skin: tachycardia, diarrhœa and excess of gastric secretion. According to Eppinger and Falta, pharmacological tests sometimes showed a preponderance of vagal tone, but sympathicotonic reactions are frequent and, together with the parasympathetic, make up a picture of vegetative dystonia.

Except that lymphocytosis and eosinophilia are common, there are no regular changes in the *blood*, but polycythæmia is sometimes found in "desiccated" cases of gastric tetany.

The *metabolic disturbances* are quite typical. Both experimentally and clinically, tetany patients are poor in calcium. Their brain contains less calcium than the normal: calcium is deficient in the blood, and the lime excretion is increased. This poverty in calcium leads to a disturbance of the electrolyte balance, and to alkalosis. In severe cases the protein metabolism is regularly disordered, and the intermediate processes of protein destruction undergo alteration. The ammonia excretion, ammonia quotient, creatinin excretion and peptide nitrogen are raised (L. Borchardt), probably on account of a derangement of hepatic function (W. Falta). Reports on the carbohydrate metabolism differ considerably, but hyperglycæmia, whether spontaneous or evoked by adrenalin, does not enter into the picture of the disease. The blood-sugar during and after the attack is low. The gaseous interchange is sometimes disordered, but the reports of observers differ about this as well. It is reasonable to suppose that cases with a lowered basal metabolic rate are hypothyroidal. Regular disturbance of the respiratory basal metabolic rate, apart from the onset, is apparently not present.

The nervous system shows that, except for those signs of hypersensitivity that have already been mentioned, typical cases exhibit no organic changes; there is no para-

lysis, no atrophy, and no changes in the cerebral nerves or reflexes. Psychically the patient remains as a rule undisturbed, but acute psychoses have been observed in severe cases, with or without inanition. Not uncommonly, patients tend to react with hysteria or neurasthenia, so that mixed cases of tetany and hysteria sometimes occur.

Of the other conditions with which tetany may be combined, one of the most frequent is *epilepsy*. On the one hand, it is seen in children and young people with thyro-hypoplasia, and the attacks of epilepsy and tetany may alternate. On the other hand, others as well as myself have observed that true epilepsy has developed from a basis of infantile spasmophilia. Moreover, epileptic attacks have been produced experimentally in parathyroidectomized animals. It is conceivable, therefore, that the course of combined tetany and epilepsy may include psychic regression and even dementia.

Tetanic stigmata (Chvostek, Erb and others) and, less commonly, attacks, are observed in cases of genuine pluriglandular insufficiency and in conditions with varying degrees of pluriglandular symptoms, such as myasthenia and myotonic dystrophy. Sometimes tetany occurs in osteomalacia and late rickets. It has been seen, though very rarely, in diseases of the basal ganglia, such as chorea, paralysis agitans and the spastic form of pseudo-sclerosis ; it also occurs sometimes in syringomyelia and poliomyelitis.

The **diagnosis** must eliminate before everything hysteria. That " great mimic " can counterfeit faithfully the tetanic attack but not the galvanic over-sensitivity (Hans Curschmann), which gives a decisive method of distinguishing between hysteria and tetany. The same test eliminates all other muscular spasms, especially those of arteriosclerosis, uræmia and pre-uræmia, meningitis, the neuritides, diabetes, strychnine and lead poisoning and other toxic conditions, besides those cases of Jacksonian epilepsy that simulate tetany.

Course and Prognosis.—In primary occupational tetany the course is usually chronic and the prognosis for health very doubtful. Out of thirty-seven cases observed by

Frankl-Hochwarts, thirty-two passed into a chronic or chronic-relapsing state. Relapses usually appear between January and April, and the disease may last for decades. I know of one case of over twenty years' standing.

The prognosis in gastric tetany is still more unfavourable; 50 to 77 per cent of patients die. The form resulting from thyroidectomy is often fatal—it was especially so in former days—and runs a shorter and stormier course. The prognosis of maternal tetany is also unfavourable, since the attack may be repeated at each pregnancy, and in other patients at each lactation. Deaths have been known to occur from this form. Tetany as a complication of acute infections and mild intoxications is generally a fleeting condition from which recovery is rapid.

The **treatment** of adult tetany demands special consideration before that of tetany in children and babies is discussed. There is an infallible prophylactic against tetany following thyroidectomy, and that is the fundamental one of leaving the parathyroid glands alone. The tetany of gastric insufficiency can be averted by early and radical measures such as irrigation or operation, and that of child-bearing by avoiding subsequent pregnancies and lactations, whichever is the occasion of the attack.

An absolutely effective substitution treatment does not yet seem to exist. For various reasons I have never been able to use parathyroid tablets, but fresh horse parathyroid has apparently worked well in very severe and acute cases. Whether the parathyro-antitoxin of Vasalle, which is probably prepared on the lines of Mœbius' "antithyroid serum", will give good results is not yet certain. The recent isolation by Collip of the active hormone of the parathyroid may well make possible an effective substitution treatment, for his parathyroid extract actually prevented experimental tetany and rendered it milder in spite of a low blood-calcium content. Transplantation of human parathyroid into the spleen, bone marrow or abdominal wall in bad strumiprivous cases, which has often been attempted, has produced excellent results, but the tetany returned when the graft was absorbed.

I myself and others have had successful results for some

years now with calcium therapy. Many cases have been cured and many others substantially improved. The indication is obvious : the lime starvation common to all tetanic patients. Naturally, especially in chronic tetany, calcium treatment must be continuous, especially as calcium given by the mouth only begins to be retained after it has been administered for a long time. Calcium chloride or lactate, not less than 3 to 6 grm. a day (two tablets of Kalzana, one teaspoonful of Glykalz or some such preparation three or six times a day), should be given. In severe acute cases intravenous injections of, for instance, Afenil, are indicated.

Porges and Adlersberg, regarding the disorder as an alkalosis, have given sulphate of ammonia, a drug which is more certain than any other to produce acidosis. The reports on its effect in adults, however, are as yet too scanty to form a basis for an opinion.

Gastric tetany, on account of its malignancy, calls for the most rapid—which means operative—treatment of the motor insufficiency of the stomach by means of the shortest operation, which is gastro-enterostomy. Patients have been shown by experience to be bad subjects for long and severe procedures. The harmless tetany which goes with bowel affections of various kinds demands treatment of the original conditions, and the same is true of the least malignant form of tetany, that which occurs with intoxications and infections. Similarly, tetany as a symptom of late rickets and osteomalacia should be treated with phosphorus; not, however, with adrenalin, which precipitates the attack. When tetany is severe in pregnancy, induction of labour at full term or before may, under certain circumstances, be indicated.

In all severe cases, rest, sometimes in bed, good nursing, and protection from psychic stress are necessary. Warm baths should be avoided, as I have often seen them provoke an attack. Cold local fomentation generally diminishes the severity. In bad acute cases the ordinary sedatives and hypnotics, and scopolamine, should not be neglected. Morphine, especially in chronic cases, is naturally to be avoided as far as possible. In very bad cases some authori-

ties have had recourse to lumbar puncture and claim good results from it ; I have never found it necessary.

The diet for cases with alkalosis should contain such foods as will increase the acid value of the intake, such as a liberal supply of meat and vegetable and fruit acids, but milk and other alkali-producing stuffs should be cut down.

In general, I may say that I have succeeded in curing even severe chronic cases with the energetic exhibition of calcium in sufficiently large doses, and I recommend it most strongly.

Infantile Tetany ; Spasmophilia

Although the common ætiology of infantile spasmophilia and adult tetany, viz. deficiency of the parathyroid, has been repeatedly questioned in recent times, yet it is impossible to doubt (E. Schiff) that " a hypofunction of the parathyroid plays a part in infantile tetany ", and that this condition is therefore to be classed among the endocrine diseases. It deserves special discussion, as it differs in many ways from adult tetany.

Finkelstein, on account of its differences from adult tetany in the later stages, describes it under the general head of " the spasmophiliac diathesis ", which also includes laryngospasm and infantile convulsions. Thiemich has shown that all three have in common the cardinal symptom of hypersensitivity, and therefore concludes that the syndromes are founded on a common basis. Spasmophilia cases show the signs of Chvostek, Trousseau and Erb, and it is noteworthy in passing that children's nerves have a higher threshold for galvanic stimulus than those of adults. In children as well as adults there is usually a more lively anodal-opening than anodal-closing contraction, and the cathodal-opening contraction shows itself particularly early (under 5·0 milliamperes according to Thiemich and Mann).

Spasmophilia affects children aged from six months to four years, and is rarer between the fourth and eighth years ; this is the time when it especially attacks children with pluriglandular insufficiency and severe rickets. The fluctuation of the morbidity (the peak at the beginning of the

year) is the same as in adult tetany, except that in children the rise starts as early as November. The disease may be a family one and inherited, and an hereditary " taint " of other nervous stigmata is common.

Symptoms and Course. — *Carpopedal spasm* is the same as in adult tetany. It comes on at different intervals, and the attacks may last for hours or even all day. They are more frequent than in adult tetany, and involve the muscles of the trunk and face (the "carp mouth" of Thiemich.) Ibrahim and others have pointed out the tetanic nature of spasms of the sphincters, cardia and pylorus, and of " heart cramp ", which sometimes causes sudden death. Especially common are simultaneous *laryngo-spasm* and convulsions. Cramp of the glottis shows itself sometimes in a dragging, crowing inspiration, sometimes—in severe cases—in laryngeal cramp that may be so serious as to lead to danger of suffocation. The breathing is very laboured and there is general unrest, anxiety, cyanosis, pallor and disturbance of consciousness, all of which reflect the severity of the condition, which not infrequently ends in death. In addition to this inspiratory constriction, there is also an expiratory one, due to spasm of the diaphragm. The attacks often occur spontaneously, especially after eating, and frequently accompany the emotions of anger and fear, sudden awakening, and similar assaults on the psychical constitution.

Fig. 17.—Tetanic spasm of the hands. (After Falta.)

It is obvious that false croup and diphtheria, laryngitis and the like, can produce very similar symptoms to those of true primary laryngospasm, but they do not produce the signs of Chvostek and Erb.

The eclampsias which are known also as *infantile convulsions*, or teething convulsions, are often, though not always, associated with the signs of hypersensitivity. They resemble true epilepsy, but are exactly similar to the eclampsia of pregnancy and nephritis: after an aura lasting a varying length of time, with malaise, depression and the like, the patient loses consciousness and the eyes stare fixedly or develop strabismus. Then there occur first tonic and then clonic spasms of the whole musculature, with rotation, jactitation, etc. Tongue-biting, foaming at the mouth and self-injury are rarer than in true epilepsy, and the post-paroxysmal sleep does not usually occur. In convulsions, as in genuine epilepsy, there are petit-mal attacks, which manifest themselves in turning up of the eyes, grimacing, clicking and movement of the jaw, and motiveless rotation and flexion of the limbs, with secondary loss of consciousness.

The typical attacks only last a few minutes and recur at varying intervals; in many cases ten to twenty times a day. Sometimes, however, the spasm is continuous all day, and the patient dies in status eclampticus.

As a rule, convulsions, like other manifestations of the spasmophiliac diathesis, do not persist beyond earliest childhood, say about the third year of life. In rare cases, however, they have been observed to continue to the sixth or eighth years. I am one of those who hold that infantile spasmophilia can pass straight into true epilepsy, which is called the "spasmophiliac epilepsy" of older children and adolescents.

Of the **complications** of spasmophilia the foremost is rickets, which Kassowitz described some time ago as an indirect cause of tetany, and for which he traced the same yearly curve of morbidity. In face of the indubitable fact that the sensitivity of the nerves depends on the calcium metabolism, and that cure of rickets brings about cure of spasmophilia, the connection between the two conditions is

beyond debate. It is to be noted, however, that there are spasmophiliacs without demonstrable rickets. The frequent defects in the enamel of the incisor teeth are pre-eminently the result of tetany and not of rickets ; Erdheim succeeded in producing them in parathyroidectomized rats.

The **prognosis** in the majority of spasmophiliac cases is favourable for life and health ; the mortality depends on the constitution of the child, and still more on the treatment. Formerly it used to be high in breast-fed infants, 25 per cent and over (Escherich). The future development of the spasmophiliac child is threatened with a physical and mental backwardness, which is not rare, and with the tendency to manifest a wide range of neuropathic traits.

Pathogenesis of tetany and spasmophilia.—The rôle of the parathyroids has been established by many clinical and, more important still, by many experimental findings. Their removal from animals leads inevitably to tetany (Vasalle and Generali and others), to signs of over-sensitivity and to multiple trophic disturbances in the teeth, hair, lenses (cataract), skin and other organs (Fr. Pincles). Tetany only occurs in thyroidectomized patients when the parathyroids are extirpated with the thyroid. There is no record of histological change in most of the cases of infantile and toxic and of gastric insufficiency recorded in the literature.

The effect of the parathyroids on the calcium metabolism is a very profound one. It is probable that the tetany-producing factors are derived for the most part from a disorder of the relationship between the calcium and potassium ions, especially from an insufficiency of the former. How this happens, how hypoparathyroidism leads to calcium poverty and tetany, was for a long time a matter of dispute. Recently, however, it has been established that the blood of parathyroidectomized animals and spasmophiliac children is rich in amino-bases, especially dimethylguanidin. E. Frank succeeded in producing in cats actual tetany, with the essential signs of hypersensitivity, by administering this poisonous substance. He concludes that the guanidin, in fixing itself in the living substance, somehow breaks up the attachment of the calcium to the plasma colloid and pro-

duces calcium shortage ; the consequent disturbance of the normal electrolyte balance increases the sensitivity of all nervous organs and leads to alkalosis of the blood.

Recent writers have tended to lay the greatest stress, especially in infantile spasmophilia, upon the alkalinity of the blood, and to conclude that it is the fundamental cause of genuine tetany in all cases, denying that place to parathyroid insufficiency, which is not invariably present. We must admit that the possibility of evoking true tetany by hyperventilation supports the alkalosis theory, for this procedure would naturally reduce the carbon dioxide content of the blood and lead to alkalosis. This "hyperventilation" tetany was first described clinically by myself, later on by Grant, and Goldmann published an accurate account of it, elucidated by experimental data. Its import is that the calcium deficiency can be caused either by an excess of guanidin or by primary alkalosis, the result in either case being tetany or spasmophilia. This explains the large number of cases of, for example, infantile and occupational tetany, in whom no histological change had been found in the parathyroid ; naturally, however, the absence of such changes does not necessarily prove that the gland is intact.

The question of diet now plays an all-important part in the pathogenesis of infantile spasmophilia, as opposed to the tetany of adults. The former is now considered to be the product of an alimentary auto-intoxication ; cows' milk is especially liable to favour tetany, which is only rarely seen in breast-fed infants. Finkelstein states that the toxic principle is contained in the whey of cows' milk. The derangement of the calcium metabolism, and the abnormal calcium-reducing effect of the alkalosis produced in this way by the diet, also finds expression in rickets, the vitamin-deficiency disease which is typically associated with tetany. Measures which help calcium-retention, such as the administration of the cod-liver oil vitamin with phosphorus, affect both spasmophilia and rickets.

The **treatment** of infantile spasmophilia is therefore on the one side (and chiefly) dietetic, and on the other side medicinal. In babies it consists in the withdrawal of cows'

milk and its replacement by breast milk. In many cases the bowel should be completely emptied and a short course of barley-tea [1] should be given. Quite good results have been obtained in case of need by using cereal preparations (such as " Kufecke "). In children of nine months or over a judicious course of cod-liver oil and phosphorus may be tried. In older spasmophiliacs with manifest rickets it is the treatment of choice. Artificial sunlight is especially good as a specific for alkaline disorders, but how far milk irradiated with ultra-violet rays—recommended by American authorities as a substitute for the anti-rachitic vitamin—will prove effective in practice remains to be seen. Of recent years some workers have used sal-ammoniac against alkalosis with distinct success (Freudenberg, György) ; hydrochloric-acid milk is also recommended. Others besides myself have obtained excellent results in spasmophilia with calcium treatment (see p. 57), which is more effective in relatively large doses : 3 to 6 grm. of calcium chloride, for example.

When the eclamptic attacks become so frequent as to be dangerous, chloral enemata or small doses of luminal or sodium-veronal may be given, often with good results.

Preparations of parathyroid gland have hitherto failed with children, but Collip's hormone may possibly be the medium of an effective substitution therapy for them as well as for adults.

Spasmogenic Dyspepsia

Under the name of spasmogenic dyspepsia or disturbances of nutrition, certain Japanese authors and Reyhe have described a syndrome which includes most of the nervous and physical dystrophic disorders of ordinary spasmophilia, but the hypersensitivity signs of Erb, Chvostek and Trousseau are generally absent. The disease is referred to a deficiency of the anti-neuritic vitamin B, and is probably akin to the beri-beri of infants. If calcium deficit and rickets are added to the picture, a complete

[1] Translator's Note.—There is no English equivalent for this " *Tee-schleimdiät* ". It is a tea and barley-water mixture given to children ; it has a diuretic effect and is one of the numerous " teas " extensively used on the Continent. Cf. Fr. *tisane*.

spasmophilia with the signs of hypersensitivity due to calcium shortage may result.

The morbid anatomy of this condition reveals, besides dropsy, atrophic changes in nerves and muscles, and cardiac dilatation and hypertrophy, especially of the right heart. Changes in the parathyroids are inconstant and probably incidental. This vitamin-deficiency disease should yield to the liberal administration of vitamin B (especially in yeast); breast milk is recommended, and a mixed diet should be commenced as early as possible.

Hyperparathyroidism

Many diseases have been ascribed to hyperfunction of the parathyroids, sometimes on purely speculative grounds and sometimes because hyperplastic parathyroids have occasionally been found in them. As examples, tetany belongs to the former group, and rickets, osteomalacia and other bone diseases to the latter. These observations are entirely hypothetical and undemonstrable; in actual fact nothing certain is known about hyper-parathyroidism in man. To the symptoms of hypercalcæmia of high grade, as produced experimentally, there is as yet no counterpart in human pathology.

DISORDERS OF THE PITUITARY

Anatomy and Physiology.—The hypophysis cerebri (cerebral appendage or pituitary gland), a structure barely the size of a pea and half a gramme in weight, lies at the base of the skull in the sella turcica. As we shall see, changes in the sella turcica, as revealed by X-rays, are of extreme importance in diagnosing pituitary tumours. The pituitary gland consists of two parts which differ completely, both in the history of their development and in their function: the glandular anterior lobe and the nervous posterior lobe. The anterior lobe imparts its secretion to the blood-stream; the posterior is in direct connection with the third ventricle through the infundibulum. The anterior lobe is recognizable as a gland by its epithelial tubules, the cells of which are of different kinds, including eosinophils. The posterior lobe consists of glial tissue, nerve fibres and ganglion cells. Between the two parts there lies an intermediate stratum (pars intermedia) similar in structure to the thyroid and bearing a direct relation to its function, for its experimental extirpation causes the thyroid to hypertrophy.

The close anatomical connection of the pituitary, especially of its posterior lobe and infundibulum, with the floor of the third ventricle and the tuber cinereum, accords with the functional relationship which recent investigation has amply proved that it bears with the metabolic and vegetative centres of the hypothalamic portion of the mid-brain. Clinical and experimental results have shown that certain lesions, whether they affect these subthalamic centres or the stalk or posterior lobe of the pituitary, can produce the same disorders of metabolism. It may therefore be concluded, for example, that the toning-up of the centres which lie in the subthalamic region and control the fluid economy and the fat-metabolism is effected by the pituitary (Falta), very probably by way of the "secretion tracts" of the infundibulum. This explains why pituitary secretion has been found in the cerebro-spinal fluid.

The functions of the different parts of the pituitary correspond to the structure, but have not yet by any means been completely elucidated in the laboratory and clinic. The anterior lobe, the hormone of which is known as pituitrinum glandulare, has indubitably a potent influence upon the growth and stature of the bony skeleton and soft parts alike (cf. gigantism, and the hypertrophy of the extremities that occurs in diseases of the anterior lobe, in acromegaly and gigantism). Apart from this, both anterior lobe and pars intermedia are connected with the form and function of the genital apparatus (cf. the increase in the size of the anterior lobe which occurs in pregnancy and the genital atrophy or insufficiency which occurs when that lobe is damaged), with the gaseous interchange (cf. rise of the specific dynamic value of protein in hyperfunction) and with the temperature.

The hormone of the posterior lobe and infundibulum (pituitrinum infundibulare) exercises a constricting influence on the uterus and the arterial system, leading to increase of blood-pressure and reduction of urine excretion. It also reduces the fat-content of the blood and (probably) raises the respiratory basal metabolic rate. Although these conclusions seem to be well authenticated, certain results which appear to contradict them must be taken into account. The excision from an animal of the posterior lobe and, as some say, even of the whole gland, produces no symptoms whatever. Against this, however, both clinical and laboratory experience have shown that the destruction of the anterior lobe leads—after a long time, of course—to fatal cachexia (cf. the pituitary cachexia of Simmonds).

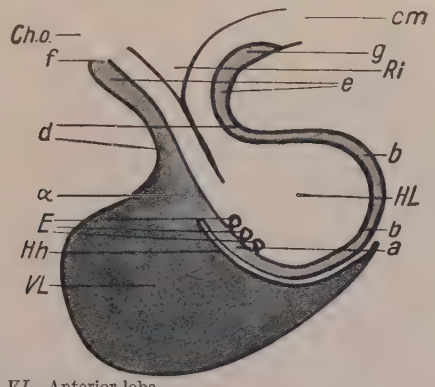
The following disease-pictures are referable with some certainty to the pituitary and its correlations with the hypothalamus: acromegaly and many forms of gigantism ; pituitary obesity (dystrophia adiposo-genitalis) ; cerebral obesity ; pituitary cachexia ; pituitary dwarfism and diabetes insipidus.

Acromegaly

This rare disease, which was first described by Verga, Friedreich and Langer, shows itself in a gradual increase in the size of the distal parts of the body, especially the head and extremities. The internal organs and the bony system are sometimes affected and sometimes not, but what is almost

always found is a tumour of the pituitary, which leads in its turn to local and general brain symptoms.

Symptomatology.—In the third to the fifth decade—rarely before—there develops a *lengthening and a thickening, usually symmetrical, of the distal portions of the body.* The process is so gradual as often to escape, at any rate in the early stages, the notice alike of the patient and his associates.



VL. Anterior lobe.
HL. Posterior lobe.
Hh. Pituitary cleft (intraglandular cleft).
Ch.o. Optic chiasma.
c.m. Corpora mammillaria.
RI. Infundibular recess.
a. Pars intermedia.
E. Ingrowth of the intermediary tissue into the posterior lobe.
b. Intermediate pallium of the posterior lobe.
d. Pars peduncularis.
e. Pars tuberalis.
f. Lobus chiasmaticus.
g. Lobus præmammillaris.

FIG. 18.—Diagrammatic section of the pituitary. (After G. Bayer.)

In some patients the hands and feet, in others the face, especially the nose, chin, zygomatic arch, orbit, and frequently the tongue, hypertrophy first. There is no local pain, but acroparæsthesias are common. At the same time there develop general debility, flabbiness and derangement of metabolism, with the frequent result, in the early stages, of obesity and in the later stages of the gradual development of cachexia, polydipsia and polyuria ; sometimes also of glycosuria and a whole range of specific brain-symptoms, such as disturbance of vision, hemianopsia, paralysis of the eye-

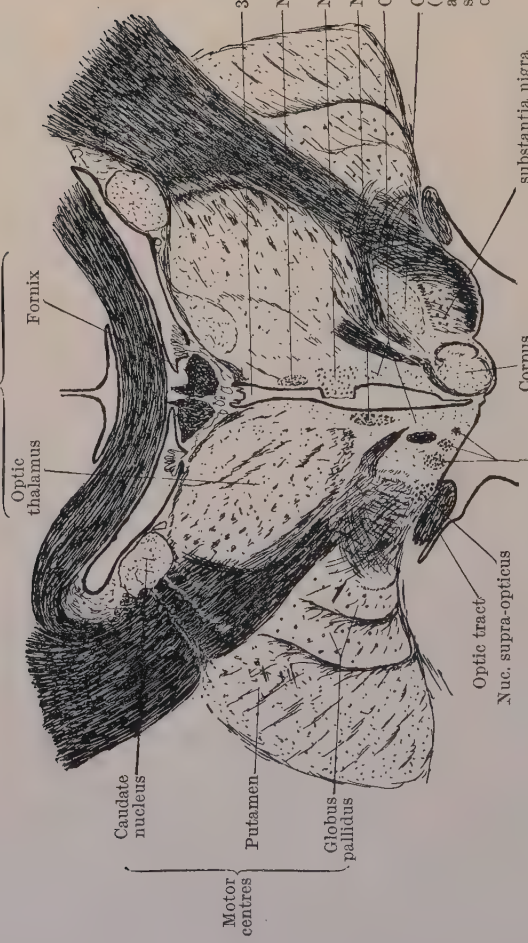


FIG. 18A.—Schematic presentation of the centres situated about the third ventricle, with respect to their function. The frontal section is oral on the left side, but on the right is more caudal.

muscles, headache, vertigo, vomiting, and finally severe psychic regression.

The **clinical picture** at the height of the illness is roughly as follows : the general impression is that of an exhausted giant. Patients have often an extraordinary *length of body* ; this is partly because the disease tends to attack particularly

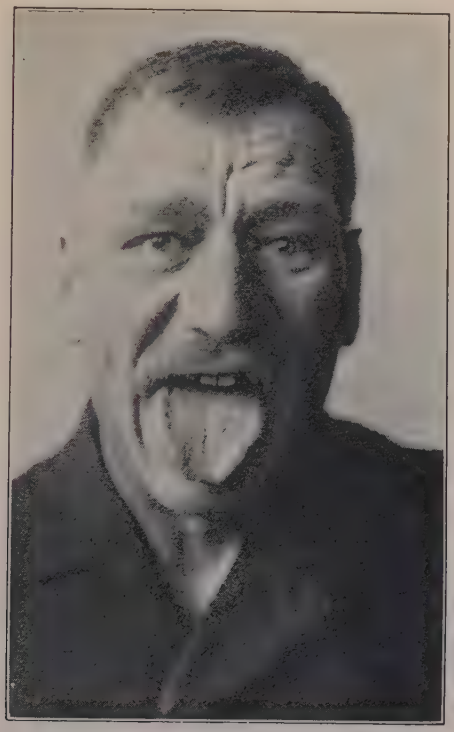


Fig. 19.—Macroglossia in a case of acromegaly. (After Grote.)

tall people, and partly because of the increase in height which results from any illness in adolescence. The face is much disfigured and coarsened. The nose and chin, as well as the lower lip, are as a rule especially thickened and lengthened, and the ears and supra-orbital and zygomatic regions share in the general increase in bulk. The upper lip and upper jaw, however, with the brow and skull, often remain normal,

although they too may be hypertrophied. The occipital protuberance is practically always very much thickened. Of the buccal organs the tongue is almost invariably thickened and lengthened, but the other soft parts, especially the pharyngeal ring, are often spared. Changes in the hands and feet are often very noticeable, especially by the patients themselves. The hands become huge, and as a rule resemble

Fig. 20.—"Spade hands" in acromegaly, compared with a norma pair. (After Grote.)

soft, pallid paws. Their breadth and thickness are usually increased disproportionately, but occasionally the hands grow in length only (P. Marie's types "en long" and "en large"). In spite of this, and in contrast to the macrocheiria of syringomyelia and drumstick fingers, the nails generally remain normal. Similarly the feet increase in length or breadth or both, and disfigurement of the great toes is apt to become especially grotesque. The hypertrophy of the hands and feet is often made much more conspicuous by

the forearms and legs remaining normal, or even, at the height of the disease, becoming thin from muscular atrophy. The recent anthropometric investigation of a case established that the pathological growth affects not only the extremities

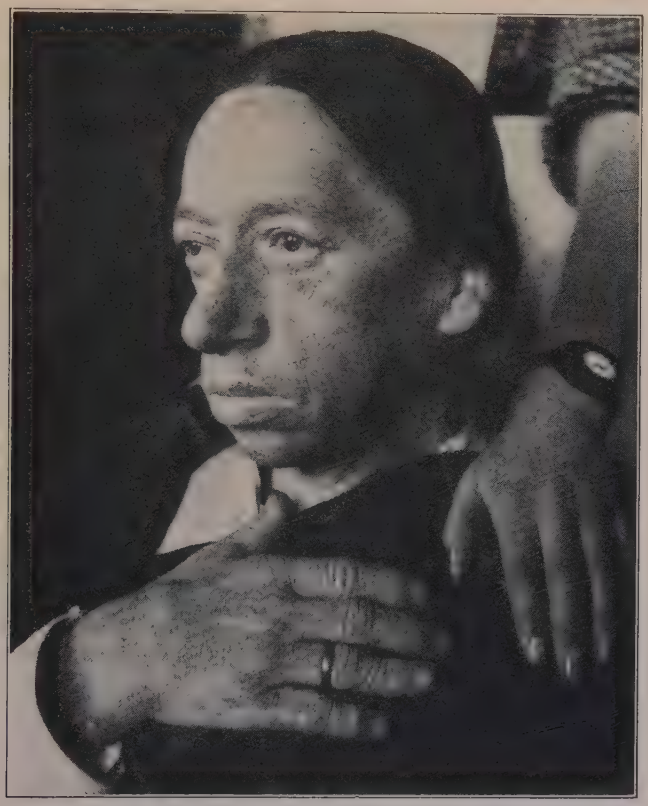


Fig. 21.—Acromegaly, with especially characteristic nose, lips and hand. (Grote's case.)

but also the bones at the intermediate joints (Ballmann and Hock).

The *skin* is usually rather thickened, with coarse wrinkles, and is often abnormally flaccid, soft, lack-lustre and moist, but is sometimes conspicuously dry. It does not often undergo gross trophic and vasomotor disturbances. Anomalies of

pigmentation are seldom seen. The scalp hair, and also that of the face and trunk, sometimes falls out ; many patients retain it, but it is apt then to be scrubby, discoloured and prematurely grey. Occasionally thickening of individual hairs is noticed. In women an abnormal growth of hair on the face is often observed. Many patients, especially adolescents, develop an excessive growth of hair on the body.

Apart from the *tongue*, which is often enlarged, the digestive organs seldom show any anomalies. The mucosa of the pharynx and œsophagus is sometimes thickened, and the stomach and intestines are occasionally found to be enlarged. The larynx and vocal cords take part in the hypertrophic process, and the voice becomes hoarse and often abnormally deep. The heart also is not infrequently enlarged.

H. Zondek occasionally found hypertrophy, especially of the left ventricle, and an increase in blood-pressure. In my experience, hypotension and a heart of normal size are commoner in patients with no arteriosclerosis. Tachycardia has been recorded, and I have also seen bradycardia when there was a high degree of pressure on the brain.

In many cases there is also enlargement of the liver, spleen, kidneys, pancreas and organs of the nervous system. The genitalia of the adult male often hypertrophy from the start ; later, though usually quite soon, both male and female organs atrophy and all sexual function is lost.

Metabolism is often disordered. Polydipsia and polyuria (diabetes insipidus) are especially common, and diabetes mellitus is sometimes seen ; its origin in many patients can be shown both clinically and anatomically to lie in the pancreas. The blood-sugar is often increased, without glycosuria, and rises very readily on the administration of adrenalin. There is a rise in the minimal protein consumption, and a tendency to nitrogen retention. The system also tends to retain chlorine, lime and phosphorus, but in many cases the blood-calcium is found to be lowered. The respiratory exchange may, it seems, remain normal (H. Zondek), but a slight rise in the basal metabolic rate (14-18 per cent)

and a slight fall have also been recorded. The specific dynamic action of protein on the basal metabolic rate appears to be reduced. The excretion of endogenous uric acid has been found by W. Falta and Novaszinski to be raised. Apart from an unspecific lymphocytosis the blood shows nothing out of the ordinary. In cachectic patients I have often observed a typical secondary anæmia.

Fig. 22.—Acromegaly (the same patient as in Fig. 21). (Grote's case.)

Most important of all the findings are the *changes in the pituitary*, usually in the glandular anterior lobe. There is generally a benign adenoma and only very occasionally a malignant adenocarcinoma; sometimes there is a pure strumous transformation. The tumour may reach the size of a walnut. It usurps the sella turcica, especially its posterior part; the widening and modification of the shape of the sella that appear in an X-ray photograph constitute an exceptionally important positive sign. Sometimes the tumours grow deep in the sphenoidal sinus; many spring from ectopic pieces of pituitary in that region, and it is these which cause the local and general brain symptoms of acromegaly. Pressure on the chiasma of the optic nerve elicits the sign, which has now been known for a long time, of bi-temporal restriction of the visual field, at first asymmetrical and partial, but later becoming complete. Sometimes, however, the widening of the sella turcica and all eye symptoms are absent.

The ophthalmoscope generally reveals partial atrophy, rarely a choked disc. Occasionally pressure lesions of the trigeminal and oculo-motor nerves—usually paroxysmal—manifest themselves. The general symptoms of cerebral pressure are those usually associated with intracranial tumours: headache, vertigo, vomiting, malaise, bradycardia, and finally mental deterioration. As a rule the general and local cerebral disturbances fluctuate considerably in their intensity. They are liable to undergo long remissions, and in the early stages of the disease may be absent altogether.

Other endocrine disturbances are fairly common. The genitalia usually atrophy, and their function is disordered very early. It is by no means rare for acromegaly to be conjoined with goitre and other symptoms of Graves' disease, but it is more commonly associated with signs of myxœdema, accompanied by atrophy and sclerosis of the thyroid. The adrenals, thymus and pancreas often hypertrophy at the onset of the disease.

Other nerve lesions are rare and uncharacteristic. The thickening of certain cerebral nerves which is occasionally found—*e.g.* of the acoustic or facial—does not cause any gross symptoms. Peripheral neuritic paralyses and neuralgias are unusual. The tendon reflexes are those of cerebral pressure; they are sometimes accentuated, but sometimes diminished or obliterated. Derangements of the vegetative system show themselves now and again in vasomotor and secretory anomalies.

The *bony skeleton* shows consistent changes, especially hypertrophy of the skull, sternum, extremities, pelvis, etc. I have also seen atrophy in skiagrams of the distal bones of the extremities of patients in a cachectic condition.

Incomplete forms of acromegaly also occur. Ehrmann has described cases of "acromegaloidism" with mild symptoms and a harmless, unprogressive course. These "acromegaloid" types are familiar to every doctor; they are probably conditioned by functional disorder of the pituitary. Cases of partial acromegaly have been described in which certain parts, like the tongue or toes, have hyper-

trophied more than the rest, whether or not the general condition has come to a standstill.

Pathogenesis.—Most authors see the cause of acromegaly in a hyperfunction, perhaps also a dysfunction, of the glandular part of the pituitary, usually the result of a tumour of the gland. The results of experimental research support this theory. There exist, however, typical cases of acromegaly without pituitary growths, and adenomatous pituitary tumours without acromegaly. The latter are easily explained by suggesting that the tumour does not bring about an increase in the function of the gland ; the former have given rise to the theory that acromegaly is the result, not of alteration in function caused by the pituitary tumour, but of its pressure on the subthalamic centres of the mid-brain. Acromegaly without tumour of the cerebral hypophysis is explained by Aschner as the result of a primary lesion of the mid-brain, and cases of unilateral acromegaly seem to accord with this view.

The results of **treatment**, however, strongly support the theory of pituitary origin. Only measures directed towards the pituitary, such as its removal by the operation of von Eiselsberg, von Hochenegg, and others, or accurate irradiation by deep X-rays—a method which has recently become famous—have so far brought about cure. Internal, even organo-therapeutic, remedies are useless.

The **differential diagnosis** is always simple in well-marked cases. The enlargement of the extremities, the local and general cerebral symptoms, especially the broadening of the sella turcica and the bilateral temporal hemianopsia, the hypogenitalism and the terminal cachexia, belong to no other disease. Incomplete cases of acromegaly may be confused with certain cases of syringomyelia and macrocheiria, or of myxœdema. The leonine facies of many lepers bears a remote resemblance to cases of acromegaly with physiological or eunuchoid gigantism, but must be distinguished from it (if only for therapeutic reasons!). The same is true of patients with partial (non-pituitary) gigantism, for instance, of one limb or part of a limb. Easier still is the distinction from hypertrophic osteoarthropathy (P. Marie) with drum-

stick fingers ; and from the similar knotty distortion of the extremities and nails in diseases of the heart and lungs, and in the osteitis deformans of Paget ; from diffuse hyperostosis or leontiasis ossea (Virchow), " cranium progeneum " (L.

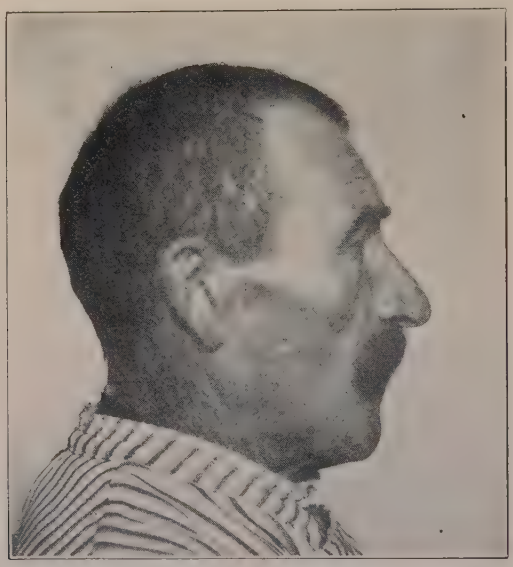


Fig. 23.—Acromegaloid type ; other signs of acromegaly, especially those associated with the pituitary, are absent.

Meyer), and other rare bone diseases. The appearance of the hand and face in achondroplasia, which is of course nearly always associated with dwarfism, may sometimes be reminiscent of acromegaly. If, however, adequate attention is paid to the primary pituitary symptoms, the diagnosis in all these cases is generally easy.

Early Acromegaly

Falta classified under this heading cases in which acromegaly began in childhood or adolescence. It is certain that these patients undergo an abnormal growth in height or gigantism far in excess of that of late acromegaly. On the other hand, it is noticeable that their extremities are

not so grotesquely lengthened. Many side-show giants are cases of juvenile acromegaly. The stimulus to growth, which arises from the alteration in pituitary function, naturally has a different effect on persons whose epiphyseal junctions are not yet closed from that which it has on those whose symphyses are fully knit : the growth in height tends to be more general. Since the lower limbs are especially long, the proportions become similar to those of eunuchoid tallness. If the genitalia remain infantile—as they often do—the similarity is enhanced. Cases in the two groups are often hard to distinguish, especially if the acromegalic type of face, as in many cases of early acromegaly, is only slightly marked. The only reliable method of differentiation is to establish the existence of the pituitary signs of true acromegaly.

Recently, however, it has been established that abnormal height does not depend unconditionally upon early acromegaly. Cases have been observed of typical acromegaly occurring without abnormal height in growing patients, and even of premature closing of the epiphyseal junctions. This, however, seems to be exceptional, and gigantism in early acromegaly is the rule.

Congenital syphilis has been found recently in individual patients, but most cases give no hint whatever of their ætiology.

Gigantism and Abnormal Height

It has already been pointed out that many giants are acromegalic, and the disease is in fact especially frequent in the tallest giants, those of seven feet and over. The " Alsatian peasant ", the largest authenticated giant in history, whose height was close on 8 ft. 10 ins., was a case of acromegaly. Sternberg estimated the proportion of pituitary giants at about 40 per cent, and it is probably even greater. A smaller group of giants, who as a rule do not exceed the two-metre limit, comes under the heading of " eunuchoid tallness ". Another and still smaller division consists of persons who suffer from no recognizable—even endocrine—pathological changes. The " langen Kerle "—" tall chaps "

—of Frederick William I.'s Potsdam Guard were, if one can trust the portraits, giants of this kind, free from endocrine abnormality. The tallest normal giant was Virchow's patient Winkelmeyer, who measured 7 ft. 6 ins. It is noteworthy that in such cases of physiological gigantism the influence of heredity is nearly always demonstrable. This family gigantism is not uncommon in pure Nordic families ; the noble houses of North Germany are an example. This is in contrast to eunuchoid and pituitary tallness, which occurs, as often as not, in families of normal average height.

Ætiology.—The scarcity of the war years and after showed it to be highly probable that abnormal tallness is encouraged by a relatively deficient diet. This phenomenon probably has some connection with the effect which a certain degree of under-nourishment has in delaying puberty, whereby the epiphyseal junctions remain very widely open. As a rule, of course, dietetic tallness only affects those who inherit a disposition to grow excessively tall. Though some of them have a normal sexual development, acromegalic giants are usually characterized by a more or less marked hypogenitalism, albeit never of so low a grade as the aplastic or hypoplastic or the eunuchoid conditions. Nevertheless, individual cases of acromegaly and eunuchoid gigantism are apt to bear a very close superficial resemblance to one another, and there are some instances in which the hypogenital and the indistinct pituitary symptoms are so closely mingled that even a minute examination fails to detect the actual origin of the gigantism.

The **differential diagnosis** is, however, of great practical importance, for the acromegalic giant needs treatment for his pituitary tumour, while the eunuchoid patient merely requires gonadal preparations. Moreover, the prognosis in the endocrine case differs from that in the healthy. Acromegalics hardly ever reach old age, but succumb either to the tumour or to the accompanying diabetes or to some incurrent infection such as pulmonary tuberculosis. Eunuchoids also do not live very long, but are always liable to illness. Normal giants, however, show for the most part no tendency to a short life.

Another form of pathological gigantism is that which occurs in patients who contract Graves' disease in their years of growth (Holmgren) ; they are mostly of the long-legged eunuchoid type. Sternberg mentions the following very rare forms : multiple neoplastic exostoses (leontiasis ossea) ; hemi-hypertrophia facialis ; multiple rachitiform curvatures of the bones, such as are seen in cases of Paget's disease or hereditary syphilis and which may well be determined by the pituitary or the centres which correspond to it. Children with tumours of the testicles and the pineal gland suffer from premature sexual development accompanied by abnormal and premature tallness ; since, however, this is succeeded after a certain time by the union, also premature, of the epiphyseal sutures, their final height is not abnormal. On the contrary, they are sometimes rather short.

The **pathogenesis** of gigantism and excessive tallness is therefore not uniform. It is certain that hyperfunction of the pars glandularis of the pituitary plays the most important rôle and produces the tallest giants, but the close relationship of eunuchoidism, both early and late, of dietetic factors (which contribute actively by bringing about delayed sexual maturity), and of Graves' disease to pathological tallness, suggests that there is quite possibly a pluriglandular factor. Falta may well have been right when he concluded that gigantism was the result of a predisposition to excessive growth which was inherent not only in the whole endocrine system, but also in the rudimentary germ plasm of all the bodily organs.

Acromikria

Brugsch described as " acromikria " a case in which atrophy of the extremities, especially the distal bones, occurred, together with genital atrophy and diabetes insipidus. X-rays showed changes in the sella turcica, and Brugsch concluded that there was aplasia of the anterior lobe of the pituitary. The combination of acro-atrophy with diabetes insipidus and atrophy of the genitalia makes it in fact quite permissible to postulate a pituitary (or mesencephalic) process with exactly opposite symptoms to those of acromegaly. Nevertheless, the physician should remember that acro-atrophy of the bones also occurs in other

diseases which are certainly not pituitary, such as sclerodermia, chronic benign Raynaud's disease, and, more especially still, polyarthritis deformans. He should be very sparing and cautious with this new diagnosis.

Pituitary Obesity: Dystrophia Adiposo-genitalis

This rare condition, originally described by Fröhlich in 1901, begins in childhood and is commoner among boys than among girls. It sometimes runs in families, and occasionally appears in stocks with a tendency to physiological corpulence.

Fig. 24.—Boy of 11 with dystrophia adiposo-genitalis, with marked genital hypoplasia. (Fr. Prange's case.)

Symptoms and Course.—Its course is generally very slow, and it is often mild for a long time at the beginning. The *obesity* and the *cerebral symptoms* usually develop very slowly and insidiously, and may continue for a long time before they are recognized as morbid. In some cases, however, they take an acute form. The fat is distributed as in well-nourished infants: the abdomen, buttocks, hips and breasts are covered and the extremities left bare. The face is round and doll-like. The skin is soft, like a baby's, and is sometimes pallid, but the blood does not as a rule show any signs of anæmia. The *genitalia* usually remain more or less infantile and under-developed, and aplasia of the testes and cryptorchism are common. Some patients have outwardly normal

genitalia, but the function is nearly always disturbed. There also appear symptoms of cerebral disturbance of pituitary origin : general symptoms of cerebral compression (pressure, pain, vertigo, vomiting, giddiness, etc.) on the one hand, and local symptoms (disturbances of vision, bitemporal hemianopsia, papillitis or atrophy) on the other. Broadening, disfigurement, and even destruction of the sella turcica, are often revealed by X-rays. As in acromegaly, there is sometimes diabetes insipidus, and more rarely diabetes mellitus.

Fig. 25.—Dystrophia adiposo-genitalis in a girl of 13. (Author's case.)

The *metabolism* shows comparatively few changes. The blood-sugar is as a rule normal, and its rise in response to adrenalin varies. Experiments on the gas-interchange have generally given a normal basal metabolic rate, and the specific dynamic action of protein was nearly always found to be lowered (Kestner and Plaut); otherwise there was no specific stigma of a supposedly pituitary obesity. The heart and circulation usually show no anomalies.

The height is as a rule normal. Eunuchoid tallness is generally absent, and some patients are shorter than the average. Acromegalic changes in the head and limbs, and gross disorders of the bones, joints and muscles, are practically never seen. Knock-knee, however, is very common.

The mental outlook may remain intact, but disturbances, and even dementia, sometimes occur, especially in syphilitic patients. The disease is sometimes combined with the symptoms and metabolic disorders of myxœdema, and, though very rarely, with marked pluriglandular insufficiency.

Pathogenesis.—Fröhlich and others believe that the condition is due to a functional defect of the anterior lobe of the pituitary resulting from tumour formation. The disease is, however, also found in the absence of pituitary tumour, in cases of tumour of the infundibulum, the base of the brain, and neighbouring parts. This has led to the belief that, as in acromegaly, diabetes insipidus, etc., the true cause lies, not in the pituitary lesion itself but in the pressure effects which it exerts on the hypothalamic centres of the mid-brain which control metabolism. H. Zondek is probably right, however, when he combines the pituitary and the mid-brain theories and concludes that "disturbance of the hormonic interrelation between the pituitary and the hypothalamic region is the primary factor in determining the disorder" (meaning pituitary obesity): his aphorism would apply equally well to acromegaly and diabetes insipidus.

Fig. 26.—Cerebral obesity of Biedl's type in a spinster of 30. (Author's case).

It should be noted that syphilitic, and especially hereditary syphilitic, changes occur in association with tumours.

Cases of "cerebral obesity" (Biedl) seem to be of pure hypothalamic origin. In their early onset, slow progress, obesity, genital atrophy, metabolism and other characteristics they may strongly resemble pituitary obesity. They are distinguished, however, by the severe dysplasias, including

deformities such as syndactyly and polydactyly, by retinitis pigmentosa of various degrees of severity from amblyopia to amaurosis, and by pyrgocephaly, anal atresia or defective mental development. I once saw an otherwise complete case of this kind without genital aplasia.

This form of Biedl's is characterized by the complete absence of all pituitary symptoms. Adequate records of anatomical investigation do not seem to be extant ; it seems, however, that it can include any kind of constitutional and developmental defect. Deusch and I saw it in a girl with family polydactylia. Apart from juvenile dysplasias of Biedl's form, severe cerebral obesity sometimes occurs in syphilis of the brain and after apoplectic strokes.

The differentiation of the cerebral condition from the pituitary is of diagnostic importance, since it will be useless to give the former pituitary treatment. On the other hand, pituitary obesity, like acromegaly, may benefit from surgical or X-ray treatment of the pituitary. In syphilitic cases specific treatment is indicated, but its results are not of course very certain.

Other Forms of Endocrine and Endogenous Obesity

As an appendix to the discussion of Fröhlich's disease, and even at the risk of a few repetitions, it may be as well to mention especially the relationship between other endocrine organs and obesity. This implies, of course, a discussion of the relationship which obesity of proved endocrine origin bears to the endogenous forms, a matter which is of constant interest to the physician for therapeutic reasons.

Unfortunately, it is impossible to deal more closely here with the normal and morbid physiology of fat metabolism, and I must also give up hope of discussing the alimentary obesity which is so common ; I must confine myself to the endocrine forms of adiposity and those endogenous forms which are akin to them. As our text we will take at the start Thannhauser's saying : " In the correlation of the pituitary and sexual glands with the thyroid we possess a control apparatus which, when functioning to its limits,

protects the normal individual from the results of repletion by diverting the available nourishment more or less completely in the direction of excessive fat formation".

Any kind of derangement of these three organs of secretion or their co-operation may lay the foundation of obesity, either in its various grossly pathological forms, in endogenous "practically normal" cases, or in the familial type. This probably holds good also for the numerous cases of so-called alimentary obesity which we can assume are due to the combination of an adipose constitution, overeating and idleness.

The *endogenous obesity* of individuals who consider themselves normal has a marked familial and racial incidence, and is characterized by none of the easily recognizable metabolic stigmata and other peculiar physical and psychical symptoms that distinguish the thyroid and pituitary types. Nevertheless, it is permissible to suspect that such people are fat or become fat because of some anomaly, not amounting to disease, in the function of one or more of these glands. They show, as a rule, no manifest hypogenital or hypothyroid symptoms or pituitary or mid-brain disorders. Nevertheless, the influence of their endocrine or autonomic nervous make-up on their fat metabolism is defective and leads to the over-accumulation of fat. I think that the modern view is wrong which refers "endogenous" obesity to the anterior lobe of the pituitary alone.

If we agree, as has been said, that not a few cases which end as "alimentary" obesity have really developed from this endogenous and endocrine basis, we can form some idea of the enormous number of cases of *endocrine obesity* which exist. If we take this view of endogenous fatness it is also comprehensible that between the endogenous cases on the one hand and the grossly pathological endocrine cases on the other there must exist very many intermediate states. These are recognizable, for example, in cases of endogenous obesity with very slight functional disorders of the gonads, or in cases with slight and in no way disfiguring thyroid insufficiency; patients whose doctors would no more call them hypothyroidal than their friends would call them

invalids. Endogenous obesity of this description constitutes by far the largest group of the endocrine class, using the term in its widest sense. The grossly pathological forms are much rarer. This is true, as we have said, of pituitary adiposity and its cerebral equivalent, and also of the obesity of thyroid origin, which used to be erroneously regarded as fairly common. Nevertheless, to deny its existence altogether, as some recent authorities have done, is equally incorrect. Adiposity is a concomitant symptom of many cases of myxœdema (*q.v.*), both in adults and children, and occasionally appears as the chief or only apparent symptom of thyroidal insufficiency, and indeed as one form—though certainly an uncommon one—of partial benign hypothyroidism. I would limit the use of the term "thyrogenous obesity" to those cases in which the typical plumpness of the wrists and ankles, the equally typical myxœdematous skin and hair, the umbilical hernia, etc., are nearly or quite absent, but in which constipation, hyperidrosis, bradycardia and sensations of chill awaken the suspicion of hypothyrosis. The cardinal metabolic symptoms, such as the lessening of the respiratory basal metabolic rate in conjunction—unlike pituitary adiposity—with a normal specific dynamic protein value, the increase in serum-protein concentration, etc., are as characteristic of these incomplete forms as is their typical favourable response to thyroid extract, and affords proof of their thyroidal origin. The fat distribution in these cases seems to be a fairly uniform one. The genital function in these incomplete thyroses is not as a rule impaired, though amenorrhœa and sexual frigidity are not uncommon in women.

Therapeutically thyroid extract is specific.

Hypogenital obesity is considerably more common than the thyroidal and pituitary forms. To a certain extent it is even physiological, as, for instance, when it appears as post-climacteric corpulence in both sexes, especially pronounced in the " matronly " type. The extra fat in this form chiefly goes to the abdomen, pelvic girdle, upper arms and thighs, while the face, neck and distal parts of the extremities may

remain relatively thin or even shrivelled. In the male during involution it is usually deposited on the abdomen and the back of the neck.

Adiposity from castration in man and animals will be dealt with in a later section. In castrated animals especially it is a matter of everyday observation that endocrine obesity and obesity which is admittedly alimentary are seen in their highest degree, and that fattening occurs on a very much lighter diet.

Of importance, although rarer than post-climacteric adiposity, is the following form, which affects relatively young people with or without a familial or individual predisposition to corpulence. After a more or less markedly premature sexual maturity, hypomenorrhœa or amenorrhœa sets in, sometimes as early as the third decade, and the patient becomes sterile and frigid. At the same time adiposity appears and develops rapidly, with the same distribution as post-climacteric obesity. This premature climacteric type is much commoner in women than in men. There is also a form which afflicts women who have had a corpulent abdomen in early youth as a result of hypoplasia of the internal reproductive organs ; this variety is always accompanied by a modification of the secondary sexual characteristics or their change to the virile type.

This last-named trait is sometimes observed in obesity either of the normal or of the early climacteric type. Among women it shows itself in a male distribution of hair, the growth of a beard, deepening of the voice, and coarsening of the features ; among men in a falling of the beard, a feminine distribution of hair on the body, and a softening and smoothing of the skin. Cardiac insufficiency, arteriosclerosis, hypertonia and chronic nephritis very often constitute grave complications of hypogenital obesity, whether of normal or early involution. Vaso-dilator symptoms, such as sudden flushing, cyanosis, hyperidrosis, and sometimes polycythæmia, also occur.

The metabolic phenomena of thyroidal obesity, such as the diminution in the basal metabolic rate and the physio-

logical and psychological stigmata of hypothyrosis, are absent from pure cases of the hypogenital form. It will, however, already have been remarked that both true myxœdema and thyroidal obesity can appear after either a normal or a premature climacteric, together with all the signs of hypothyrosis.

Gonadal preparations, usually in combination with thyroid, should be tried in the **treatment** of hypogenital obesity. Dieting, even fasting, is of little value. Even in the times of utmost scarcity during the war, some of these patients could not get rid of their fat. The **prognosis** for the loss of fat is therefore on the whole unfavourable.

Local Corpulence

Under this heading we include patients who put on fat in various, usually characteristic parts of the body and remain quite normal or even lean in others. Striking and grotesque cases of this condition are very rare, but moderate degrees of it are fairly common and tend to run into the normal if unæsthetic fat-distribution of healthy persons that we see every day. A form which is relatively common in women but has not yet been reported in men is an enormous fat-deposit in the legs and buttocks, reminiscent of elephantiasis, while the rest of the trunk and the arms and face remain relatively or perfectly slender. In many cases the deposit is confined to the thighs, and in some the forearms are involved as well as the legs. The fat layer is firm and elastic, and gives the impression of a tissue rich in water.

Thannhauser succeeded in inducing a rapid and considerable loss of fluid in cases of this kind by the use of novasurol. This local adiposity sometimes runs in families ; I have seen it in mother and daughter. It is not, however, accompanied by other manifest endocrine disturbances. In many cases these partial lipomatoses occur in direct association with endocrine crises; for example, with normal or premature involution, symptoms of mild Graves' disease, or hypothyroidal disorder. For this reason H. Zondek thinks that this form as well as the others is somehow conditioned by

endocrine changes. No especial anomaly of the gas interchange or the specific dynamic effect of protein is apparent. A rise in the basal metabolic rate occurs only in hyper-

FIG. 27.—A woman of 31 with adiposity of the lower half of the body. (From H. Zondek.)

thyrotic cases, and no gross disorders occur in the other metabolic systems or in the blood. Occasionally this local fat deposit becomes particularly painful on pressure or spontaneously, without any other nervous disturbances being

manifest. This is especially so in adiposis dolorosa, a form of obesity which we shall consider later.

Treatment of this regional lipomatosis has met with little success. Thyroid preparations thin down the normal parts without affecting the fat. Patients with Graves' disease and symptoms of hypogenitalism should be treated for the underlying condition.

Lipodystrophia

This form of dystrophia with abnormal fat distribution is very rare, and has up to the present only been seen in women. It undoubtedly belongs to the same class as local adiposity ; at least I know of cases of local adiposity which have passed over into it. The syndrome was discovered by Pic-Gardare and Barraguer, and first described in Germany by Simons.

Symptoms and Course.—Its onset, which usually takes place at about the sixth year (much more rarely at puberty) is peculiar : the fat progressively disappears from the face, leaving it the appearance of a death's head, and from the whole upper part of the body, except the glandular organs, the breasts and—in many patients—the upper arms. At the same time there occurs a relative, and in fact generally an absolute, lipomatosis of the lower extremities and buttocks, sometimes also of the lower abdomen, and especially of the mons veneris. This gives the patient a most grotesque appearance ; Parkes Weber described the lower half of the body as belonging apparently to a Venus in an ultra-Rubens style, while the upper half and face look like those of a witch.

Nervous or cerebral symptoms which might bespeak an affection of the pituitary or pineal gland have hitherto not been described, but hypertrichosis, rhinorrhœa, polyuria and glycosuria have been reported. The sexual function is not usually impaired, and hyper-genitalism and marked virility seem to be absent. No regular mental changes occur ; one of my cases had a typical hysteria with frequent attacks, but another was perfectly normal both mentally and in the endocrine system.

Findings in the respiratory and other departments of

metabolism have been normal, and in one case I found a morphologically normal blood and a normal protein concentration. My patients and most others complain of subjective chill, and suffer continually from cold, blue hands and feet.

The **pathogenesis** is obscure. In the one case that came to post-mortem, that of von Sarbo, changes were found in

Figs. 28 and 29.—Lipodystrophia progressiva. (From O. B. Meyer Wurzburg.)

the corpus striatum ; it is very doubtful, however, whether they were the cause of the lipodystrophia. Klien believed that a disorder of the pineal gland occurred at the time of its physiological involution, and on that account ascribed to it a substantial influence over the distribution of fat. This view, like the other, does not appear to be very well founded, and it is at all events unsupported by therapeutic evidence. Injections of epiglandolin, especially in my cases, have proved

of absolutely no value, but in the absence of any other means of curing this extremely disfiguring malady, their properties should be further investigated. For the "death's-head" face some workers have even had recourse to cosmetic injections of paraffin.

The **prognosis** for life is favourable, for the disease brings no danger of death.

Adiposis Dolorosa

We propose to regard this syndrome, in spite of various recent attacks on the theory, as a disease *sui generis*. First recognized by Dercum, it is practically confined to women after the menopause, and is sometimes, though rarely, seen in the fourth decade or earlier. It is distinguished by the combination of the following symptoms :

(i) Diffuse or local fatty deposits.
(ii) Intense pain in the fat, either spontaneous or on pinching or pressure.
(iii) General weakness.
(iv) Nervous and mental disturbances, especially depressive.

Exogenous causes play hardly any part ; I have never seen alcoholism or syphilis among my patients.

Dercum, Vitaut and others have classified the disease—perhaps a little too schematically—into

(i) Nodular asymmetrical fatty swellings.
(ii) Diffuse, ill-defined fatty growths with a certain localization.
(iii) General adiposity of the whole body.

The third form preponderated among my cases.

Symptoms.—The *painfulness of the fat*, especially on the upper arms, shoulders and thighs, and less commonly on the abdomen and breast, is extraordinarily intense, and occurs spontaneously or on pinching, even very gently. It is bad enough to make the patient cry out and shrink away. Gait, stooping and other movements may be seriously impaired by it. Deep pressure on the muscles, joints, bones and nerve-trunks (when cautiously applied) usually causes

no pain at all, provided that the condition is not associated with bone complaints, polyarthritis or polyneuralgia, as I have known it to be. The fat cushion may also, of course, occasionally be painful in endogenous and endocrine obesity, but by far the greatest number of cases in which the fat is painful either on pressure or spontaneously belong to the group of Dercum's disease.

Fig. 30.—Adiposis dolorosa. Fat particularly distributed on the belly and thighs. (Medical Clinic, Rostock.)

In addition, these women suffer from a very typical *psychic disorder*. They are all "very nervous", and the picture is that of an incipient neurosis tending in most cases to hysteria, neurasthenia or hypochondria, and in all to marked depression. My patients, when questioned, all said they were tired of life. This depressive neurotic disposition is so common that I regard it as absolutely pathognomonic. The same holds good of the lack of physical energy, which may be very marked and completely incapacitate the patient for work.

Vegetative symptoms are anidrosis or — more rarely — hyperidrosis, dyspnœa, premature greying or falling of the scalp-hair; constipation (occasionally); angiospasm of the fingers and toes; marble skin; cyanosis of the extremities, and bleeding at the nose and elsewhere.

One of the most conspicuous endocrine symptoms is *goitre*, which is not rare. The cutaneous and other symptoms of myxœdema and those of Graves' disease are generally absent. Tetanic stigmata are quite unusual; I have only seen them once, and then without manifest spasm. I have never observed pituitary symptoms,

but Jülich has seen them occasionally. In considering its relation to the genital function it should be noted that adiposis dolorosa, like myxœdema, occurs fairly often after the climacteric and after operative or premature menopause. Some patients continue to menstruate, but are as a rule sexually frigid. The metabolic disturbances are relatively slight; the respiratory basal metabolic rate was normal in my cases and the specific dynamic value of protein was lowered. The serum-protein content, the viscosity and the morphology of the blood, were normal. The cutaneous and pulmonary excretion of water seems to be reduced (Schwenkenbecher). Water and concentration tests gave normal results in my cases.

Morbid Anatomy.—Anatomically, Falta found atrophic and other changes, especially in the thyroid, but less marked and less consistently in the pituitary and gonads. Occasionally the autopsy does not reveal any monoglandular or pluriglandular change. The fat sometimes contains perivascular infective foci and interstitial neuritides, but in some cases there is nothing wrong with it.

Ætiological evidence points to the endocrine system, especially the thyroid. Dercum himself thought that the cause lay in a dysthyrosis. It is, however, quite conceivable that the pituitary and gonads also play a part and that pluriglandular disorders and disturbances of correlation have a causal significance. It is naturally also possible that there exists a central, that is to say, a mid-brain, trophoneurosis, analogous to that in Biedl's cerebral obesity. A case of Falta's, in which a chronic hydrocephalus with the endocrine glands unimpaired was found post mortem, seems to bear out this suggestion.

For **treatment** I recommend first of all thyroid extract, in the same doses as for the hypothyroses, or where possible, in even more restricted amounts. This has already given very good results in eight cases, and the favourable effect of thyroid seems to me to be the chief piece of evidence in support of the thyroidal theory of origin which already carries more weight than any other. Naturally there are cases unsuitable for thyroid, and these should be given

pituitary, with or without gonadal substance. In any case organotherapy produces better results than antineuralgic and physiological remedies, especially hydrotherapy, which had proved useless with nearly all our patients before they were correctly diagnosed and given organotherapy. Naturally it is often necessary to combine the latter with antineuralgic and sedative measures.

The **differential diagnosis** must be made very carefully in order to avoid saddling with a diagnosis of Dercum's disease every fat menopausal woman who complains of tenderness. The distinction is easy if the physician bears in mind the typical symptom-complex.

The **prognosis,** as far as expectation of life is concerned, is favourable. Relapses, especially in the psychical and nervous condition, occur fairly often in spite of thyroid treatment, and the course is bound to be long drawn out and distressing. It is probable that an unbroken course of thyroid, continued over months or, if necessary, years, may somewhat counteract this tendency to exacerbation as it does in myxœdema.

Endogenous Emaciation

Falta describes by this name a constitutional condition diametrically opposite to endogenous obesity. *Per se*, the term has undoubtedly something convincing about it. Every physician and every layman knows emaciated persons of this description, often belonging to lean families; their food "does them no good", and they never put on fat however rich their diet may be, but remain thin up to the climacteric and often after it.

It is also indubitable that in a few cases intense emaciation, like intense obesity, so bad as to amount to an illness, supervenes without any exogenous cause such as a wasting disease or voluntary or involuntary abstinence from food.

Ætiology.—In emaciation of this kind, just as in the contrasting condition, it is necessary to look before everything else for an endocrine cause, especially for a concealed hyperthyrosis. There are cases of the kind, without oph-

thalmic or circulatory troubles or psychic changes, who show a Graves' thyroid and gastric symptoms and suffer from a high degree of cachexia. They are recognizable as hyperthyroidal by the rise in the basal metabolic rate. I have cured such patients relatively quickly by X-ray treatment of the goitre. Pituitary emaciation may also be suspected occasionally in those rare chronic cases which Reyhe and others have described as mild forms of Simmonds' disease (see next page). In the same way a pluriglandular insufficiency, for example of the Noorden type, may masquerade for a long time as plain pathological leanness. A very typical and not uncommon emaciation is that which affects young asthenic women, especially of Nordic stock, after their first or second confinement.

Fig. 31.—Emaciation in a girl of 20. Insulin followed by psychotherapy led to increase in weight of 30 lb. (Author's case.)

If, however, an endocrine basis of this kind is not demonstrable, there are no consistent metabolic stigmata in those rare cases which actually merit the description of endogenous emaciation. The presumable rise in oxidation does not reflect itself in a rise in the interchange of gases, nor does the increased protein metabolism produce a rise in the serum-protein concentration as it does in Graves' disease. Nor was it possible to find the marked hypoglycæmia which is a feature of bulimia.

The *habitus asthenicus* (and, I must expressly add, the *habitus gracilis*) is the rule. The female patients are "sylph-like" beings; they have all been bad feeders from youth, and their lack of appetite, together usually with their meagre demand for

water, are only two of a group of signs of functional debility. Whether it is permissible to apply to their condition the term " primary anorexia " (Falta), in the sense that their lack of hunger is the cause of their leanness, I consider doubtful. If it were, then we should have to include under endogenous emaciation all those patients whose leanness is due to abstinence, dictated chiefly by psychological motives, especially cases of hysterical anorexia. When Falta quotes the good results of insulin-aided diet on emaciated patients without appetite, he does not seem to me to prove that " hypo-insulinism " is one of the signs of the general deficiency of physical function. Psychotherapy alone has sometimes succeeded in awakening these patients' appetites and restoring them to a normal state of nutrition. However, even though it is not yet possible to detect " essential emaciation " by metabolic and other biological methods, it is nevertheless necessary to agree with Falta that he has the same right to diagnose it as we have to regard endogenous obesity as a special constitutional condition, and on the same criteria.

The **differential diagnosis** must of course be made with great care. All other cachexia-producing diseases, such as chronic infections, tumours, disorders of the blood and metabolism, and gross endocrine disturbances, together with psychological anorexias, must be excluded. Only then is it possible, and after adequately testing it by the constitutional history, to venture a diagnosis.

The first measure in **treatment** is to try insulin in smallish doses (10-20 units), but patients should always be given psychological treatment as well. Fresh air, a judicious nourishing diet, and that old and tried friend arsenic, are as a rule indispensable.

Pituitary Cachexia

M. Simmonds was the first to describe this very rare disease in 1916. Its onset is generally between the fourth and fifth decade, and it chiefly affects women. It is sometimes associated with severe hæmorrhage (Reyhe), sometimes

occurs after syphilis and other infectious diseases, and sometimes has no ascertainable cause.

Symptoms and Course.—It shows itself in an intense and more or less gradual cachexia, emaciation and debility, which may become extreme ; secondary anæmia, a complete loss of hair from the body and thinning and greying of the scalp-hair, genital atrophy, loss of teeth, trophic changes in the skin and nails—in short, a very marked premature senescence. The temperature is usually very much lowered ; the pulse is retarded, the blood-pressure is reduced, and the heart is feeble. H. Zondek and others found the respiratory basal metabolic rate and the nitrogen exchange unusually low, and the water- and calcium-excretion greatly reduced and delayed (naturally, since oliguria is part of the condition), although the renal concentration capacity was normal and thirst was absent. Zondek deduces from these symptoms the presence of the disease with characteristics opposite to those of diabetes insipidus.

Signs of pituitary tumour (to which reference has already been made several times) may be absent, but sometimes there is a widening of the sella turcica which may or may not be due to a very early pituitary growth. Most complete cases end fatally. In those with a syphilitic basis, however, improvement has been observed after specific treatment.

Some authors, according to Reyhe, have recently regarded certain mild cases of early senility and cachexia as incipient or benignant forms of Simmonds' disease, chiefly because they were considerably improved by "Praephyson". This view, however, and the differentiation of these cases from other endocrine cachexias, such as those due to pluriglandular insufficiency, seems to be unsound and full of difficulty. M. Simmonds found in his cases a total sclerosis or even atrophy of the pituitary. Other authors have suggested tubercular, syphilitic, and even septic changes as the cause. Sometimes the hypophysis is found to be normal even when the clinical picture of the disease is fully established (A. Simons).

H. Zondek appears to be right in classing such cases as "cerebral" and assuming the presence of direct lesions of

the metabolic centre analogous to those in the pituitary type of Biedl's obesity.

Pathogenesis.—The essential pathogenetic factor seems to lie in the destruction of the anterior lobe of the pituitary, for when that part is left intact in animal experiments the cachexia does not as a rule appear.

Diagnostically any one of the innumerable known cachexia-producing illnesses, most of which are easily recognizable, must be taken into account. Where those are eliminated the physician should think of Addison's disease, and especially of certain forms and stages of pluriglandular insufficiency. It is naturally not always possible to distinguish Simmonds' disease from these, as it may be an associated symptom of one of them. Reyhe's suggestion is a reasonable one : that a failure of the pituitary may bring about a secondary insufficiency, possibly even an atrophy, of the other glands of internal secretion. As we have said, " benign incomplete " forms of the disease should be diagnosed with great hesitancy. It should be remembered that there are individuals with a familial or personal tendency to early senile involution in whom no pituitary symptoms of any sort are demonstrable (see p. 150 *et seq.*). In doubtful cases the basal metabolic rate should be investigated, and —possibly more specific and important—the water- and chlorine-excretion should be tested for the changes described by H. Zondek.

In the **treatment** some authorities have recommended " Praephyson ", a preparation of the anterior lobe of the pituitary, which may bring about improvement in mild cases. Serious complete cases are not as a rule benefited permanently by organotherapy and, hitherto at any rate, have always died. Patients with syphilis should be given specific treatment.

Diabetes Insipidus

This illness is characterized by polyuria, accompanied by a marked increase of thirst and the intake of fluids. The amounts of urine voided are enormous ; it has a low specific gravity (between 1001 and 1005), and in pure cases it con-

tains no sugar. In my opinion it is necessary to use every practicable means to distinguish these cases from primary polydipsia—as distinguished from alcoholic dipsomania—which occurs in psychopathic patients of all kinds, from hysterics to schizophrenes. The numerous polydipsia patients who came to the war hospitals were doubtless for the most part neurotics who had the unconscious motive of getting out of the war; they often combined their polydipsia with incontinence of urine. Cases of this kind can be cured by various methods, including even suggestion; their fluid intake can be immediately reduced within normal bounds without causing any severe disturbance, and they hardly ever show any alteration of their chloride metabolism.

Course.—Real primary diabetes insipidus usually begins gradually, and only rarely appears in an acute form after brain injuries. The onset is in youth or middle age, and occasionally in childhood. Sometimes it has occurred repeatedly in the same family (Weil). In my experience, men are much more susceptible than women, but I have myself seen idiopathic diabetes insipidus in two females, probably the result of cerebral arteriosclerosis or syphilis.

Symptomatology.—Patients excrete an *inordinate quantity of urine*, usually more at night than by day. Six to eight litres is quite a usual daily amount, and many patients void as much as twenty or thirty. The urine is always remarkably light in colour, often as clear as water, faintly acid or neutral, and of very low specific gravity, generally between 1001 and 1005. Sweating or a moderate check on the patient's fluid intake does not increase its concentration, nor does the administration of extra sodium chloride, which only serves to increase substantially the volume excreted. The percentage of solid matter in a sample is naturally very small, but the total volume of the day's urine compared to the intake contains a normal, or occasionally even a slightly excessive quantity of urea, and normal amounts of phosphoric acid, creatinine, sulphuric acid, lime, etc. The presence of inosite can also sometimes be demonstrated. Grape-sugar is not present as a rule in pure diabetes

insipidus. The urine is nearly always free from protein, and contains no morbid sediment, nor usually a sediment of any kind.

This polyuria is always combined with intense thirst, which is often more urgent at night, and the excretion has to balance the enormous intake. As in normal persons, the amount of fluid swallowed slightly exceeds the amount of the urine. Always a conspicuous feature is the dryness of the skin, which has very little sweating power, and the dryness of the tongue. The fluid excretion by the skin and lungs is very much reduced.

The *general condition* in many patients—when enough water is taken in to supply the subjective demand—remains for a long while unimpaired, but many others undergo a general debility which grows constantly worse and is finally accompanied by a certain degree of cachexia. Cases with gross cerebral complications naturally manifest the appropriate local and general symptoms.

The *circulation* remains strikingly free from damage by the enormous amounts of fluid which it has to carry. Cardiac hypertrophy, as in Bollinger's " beer-drinker's heart ", is not found, nor is there any rise of blood-pressure, transient or permanent, nor any premature arteriosclerosis. The appetite is not increased. In spite of the fabulous volumes of water with which it has to deal, the stomach is neither dilated nor subject to any functional disorder. The bowel action is regular, sometimes delayed. The kidneys are clinically intact, and anatomically, like the bladder, sometimes strikingly large ; there is no granular contraction. The genital system remains physically and functionally intact in all cases but those badly complicated by pituitary anomalies, such as acromegaly. The temperature is sometimes subnormal. The blood rarely shows anæmia, but occasionally polycythæmia. The organic nerve symptoms, especially of cerebral origin, have already been mentioned (see under acromegaly). The patient with diabetes insipidus does not suffer from the neuralgias, neuritis, pruritus and other ills of which the diabetes mellitus patient is a victim. In many cases, probably because of the disturbance of sleep

by the excessive drinking, the nervous system and mind undergo severe functional disorder. The course is always chronic ; remissions sometimes occur in response to exogenous influences such as infectious disease.

The **prognosis** for the patient's health, except for very rare syphilitic cases and for those pituitary cases amenable to surgery and X-rays, is nearly always bad. The expectation of life is doubtful, since the patient is apt to succumb to intercurrent diseases such as tuberculosis. The cerebral or pituitary lesion, whatever it is, is also naturally a danger to life. Many patients, however—for instance, those with the disease in the family—have been known to live a normal span or even longer.

Ætiology.—As has been noted, diabetes insipidus has been held to be due to a failure of the kidneys to deal with a concentrated urine. For this reason, when salt is taken, patients have to excrete a larger quantity of fluid in order to get rid of it, since they cannot achieve a higher concentration of urine. From the fact that the kidneys in diabetes insipidus are intact (unlike the contracted kidneys of a similar concentration disturbance), we must assume that the impairment of their function is due to a central lesion. It has been known now for some time that diabetic puncture, or piqûre, of the floor of the fourth ventricle gives rise to polyuria and glycosuria (Claud Bernard). E. Meyer and Jungmann demonstrated the existence of a site in that neighbourhood, a lesion of which produced vigorous excretion of water and salts. Clinical and anatomical results have further established that there also exist centres in the subthalamic mid-brain which influence the water and salt economy. It has recently been confirmed that not only the kidney function but also the water and salt exchange between the blood and the tissues is regulated from these centres, and indeed, these salt and water centres seem to be separate. It has also been demonstrated clinically that they can be disordered separately, and in consequence of this a distinction has been drawn between hyper- and hypo-chloræmic cases of diabetes insipidus (Weil, Jungmann). The dissociation of the two disorders is of course very rare, and

in typical diabetes insipidus the water and salt excretions undergo equal impairment.

Clinical and experimental findings bear out the theory that disease and damage to the pituitary, especially to the pars intermedia of the posterior lobe, are of significance for diabetes insipidus. In spite of this, modern opinion will support the view of E. Leschke and H. Zondek that the real site of the disturbance is to be sought in the cerebral centres, in the disturbed correlation between the mid-brain and the pituitary. In other words, the action of impulses from a pituitary gland which has undergone morbid change upon the water- and salt-controlling centres is significant for the ætiology of diabetes insipidus. This conclusion is analogous to that which we are compelled to adopt to explain the pathogenesis of acromegaly and pituitary obesity.

The **diagnosis** must take account of the primary psychopathic polydipsias that have been mentioned. The distinction can often be made relatively quickly by the sodium chloride test: psychological patients generally react with a substantial rise in the urine concentration. It has already been mentioned that psychotherapy, and even the simple restriction of their fluid intake, will cause a considerable improvement and even cure. This contrasts vividly with the distressing and alarming abstinence-symptoms with which patients of diabetes insipidus react to the abrupt stoppage of their fluid. Some of them will even drink their own urine. It should be added that there exist transitional cases in which it is impossible to distinguish between diabetes insipidus and primary polydipsia. Patients with contracted kidneys—whose renal power of concentration is generally greater—can of course be distinguished at once from patients with diabetes insipidus by their albuminuria, sediment, cardiac hypertrophy, and hypertension.

Diabetes mellitus—in which, by the way, the daily volume of urine hardly exceeds four and a half litres—is naturally recognizable without difficulty by the urine test.

In **treatment** the first step should be to look for a syphilitic ætiology, the frequency of which has been pointed out by Ebstein, senior. Neosalvarsan, mercury or bismuth have

proved effective in many cases. I have, however, seen undoubted syphilitic cases on whom specific treatment had absolutely no effect. As in all pituitary symptoms of any kind, the surgical or X-ray treatment of the tumour is to be considered, but it must unfortunately be noted that the symptoms of diabetes insipidus may persist obstinately after an otherwise successful intervention.

In the milder cases good symptomatic results have been obtained with posterior lobe preparations, such as "Pituglandol", "Pituitrin", "Hypophysin", and "Physhormon". These remedies have been observed to bring about a rise in the urine concentration and in the amount of sodium chloride present, and a diminution in the volume. I have always had to admit, however, especially in my own cases, that this effect is very slight and transitory. There has as yet been no report of a practical substitute for the missing hormone, such as insulin to a certain extent affords. This is partly due to defectiveness and unreliability of many German preparations (P. Trendelenburg).

A diet poor in salt has naturally been recommended, and has met with a certain amount of success. Patients do not tolerate withdrawal of fluid as a primary measure, and should be spared this cruelty. For relieving the thirst opium has been recommended for a long time, and is still the best remedy. I have never found "Cesan" of the smallest value.

Pituitary Dwarfism

When the disorder of the anterior lobe of the pituitary occurs in early childhood, the other symptoms, such as arrest of the sexual development, are accompanied by an arrest of growth and under certain circumstances by dwarfism. The same result has been produced experimentally on young animals. Why cachexia is absent in juvenile patients of this kind (who may even develop obesity) is obscure. Since this form often passes unrecognized it is difficult to judge its incidence. It seems, however, to be not altogether rare in "Lilliputian troupes"; it is said to affect both sexes equally, but I am inclined to think myself that men are slightly in

the majority. In growth-arrest of pituitary origin Falta observed that the epiphyses often remained ununited and that the centres of ossification were delayed in development. The result would be the maintenance of " infantile dimensions ", in which the upper half of the body is longer than the lower (in contrast to the enormous length of the lower half compared to that of the upper in eunuchoid gigantism). This pituitary arrest of growth may undergo spurts and remissions; growth may occur even in the third decade, after the epiphyseal sutures have been open for a long time.

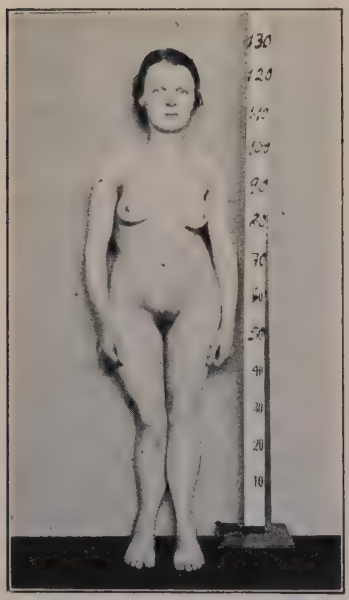


FIG. 32.—Rachitic dwarfism in a girl of 26. No hypogenitalism or infantilism. (Author's case.)

Symptoms.—The *genital apparatus* is always intimately involved. Hypoplasia of the external and internal genitalia, cryptorchism, and total or partial absence of the secondary sexual characteristics, are the rule. Obesity of the " baby " type is common. Nevertheless a premature senile shrivelling and wrinkling of the skin is fairly often noticeable in larger and older male Lilliputians.

The *respiratory metabolism* is said to be considerably reduced, and the specific dynamic protein action has been likewise found diminished or even absent. Pituitary symptoms of a localized cerebral type are remarkably infrequent; Falta has described an abnormally small sella turcica, and diabetes insipidus has been observed.

The *mental outlook* of these dwarfs is fairly good; not absolutely normal, but not in the least childish. A marked feeling of inferiority and shyness are fairly common, but many pituitary dwarfs are nevertheless very receptive and

clever. Their physical capabilities are so good that they sometimes become skilful craftsmen.

Anatomical examination of the pituitary has revealed hypo- and aplasia, post-inflammatory atrophy, and mixed and other tumours. The anterior lobe is always the more involved.

When a pituitary tumour is suspected one ought always —at least in theory—to consider X-ray **treatment** or operation, but hardly any results have been published. The good results which "Praephyson" has given in the milder forms of pituitary cachexia should encourage its more frequent use, and success has sometimes been obtained with it in this condition. Specific treatment should be administered if syphilis is suspected.

Fig. 33.—Chondrodystrophia in a female of 20. (From H. Zondek.)

The **differential diagnosis** of this form of dwarfism must involve a very brief survey of all forms of dwarfism. The following represents the nearest we can come to a discussion of those forms which are undoubtedly not determined by the endocrine system.

Other Forms of Dwarfism

If, for want of a better system, we adopt the old classification of D. von Hansemann—which has been rightly attacked because of its superficiality—we shall divide dwarfs into "proportioned" and "disproportioned". Von Hansemann includes in the latter group only those with achondroplasia and rachitic stunting of their growth. No endocrine cause has hitherto been assigned to the first form, the onset of which occurs in utero while the skeleton is still cartilaginous, and which leads to severe deformity and shortening of the limbs and trunk with an abnormally large thyro-

cephalic head. These dwarfs, the most grotesque of all, have been known from time immemorial; they used to be court jesters, and to-day they play the part of clown (" dummer August ") in the circus.

Rachitic dwarfism, which is distinguished by the typical rachitic curvature of the limbs and spinal column and the costal rosary, can only be given a brief mention. Although rickets bears a certain relationship to the endocrine system, we must regard it as principally a disease of vitamin-deficiency and poverty, and therefore as due to exogenous factors.

All other forms, especially those forms of nanism which can be demonstrated to have an endocrine origin, are classed by von Hansemann as " proportioned ".

Apart from the *pituitary dwarfism* which we are discussing, thyroidal dwarfism is by far the most common of all the types due to endocrine disturbance. It has already been described under infantile hypothyroses and athyroses, and under endemic cretinism (*q.v.*). The changes of the skin and hair, the usually gross physical defects, the disturbances of metabolism (diminution of basal metabolic rate with abnormal specific dynamic protein action), the specific blood-changes (G. Deusch and others), the changes in the bony system, the umbilical hernia, and above all, the typical amenability to thyroid extract: these generally make the diagnosis easy in pure forms of hypo- and athyrosis associated with dwarfism. Cretinism is fairly easily recognizable as the cause of dwarfism by its familial and regional incidence and its whole picture, especially the more or less pronounced imbecility. Mongoloid degeneration (as a sequel of dysplastic disturbance of the brain) also leads to stunting of growth, but only very exceptionally to dwarfism (meaning an adult height of under 4 ft.).

Other rare endocrine forms are *thymus dwarfism* and those associated with adrenal and pancreatic insufficiency. In the thymus dwarf the skin is pasty; there is hyperplasia of the thymus and the lymphatic system and signs of a more or less manifest tetany. The mind is sluggish and obtuse, and there is a tendency to eczema and a retardation of sexual

development. The results of extirpation of the thymus in young experimental animals have demonstrated the possibility that a diminished activity of the thymus may be a cause of dwarfism in man.

Gross *pancreatic insufficiencies* usually lead to combined

Fig. 34.—Infantile dwarfism. A boy of 11, of approximately the same size as his three-year-old brother, who is standing beside him. He is thin, but well-proportioned. He is a clever and good-natured child, and his lively and mature expression contrasts with the anxious look on the face of his brother. (Author's case.)

diabetes and infantilism, and only rarely to dwarfism. Disorders of adrenal development may also, in very rare cases, give rise to dwarfism and not to premature genital and other development. No symptomatology or diagnostic rules can be laid down for this form.

The *dystrophic forms* of arrest of growth, those for instance which follow exogenous damage such as syphilis, tuberculosis, malaria, pellagra and severe disturbances of nutrition, are generally classifiable as infantilism (*q.v.*) and not as true dwarfism.

There now remain only two of the "proportioned" forms: *primordial* and *infantile dwarfism*. The ætiology of both is quite unknown, and there is no evidence, even the flimsiest, to show what endocrine factors enter into it. Both are typical examples of the "healthy" dwarf. They can only be distinguished when an adequate history—*i.e.* one supplied by the mother—is forthcoming. The primordial dwarf is abnormally small at birth (the case reported by Virchow and von Hansemann weighed only 500 g.) and grows very slowly and imperfectly, sometimes in remarkable spurts. The respiratory metabolism, heart, blood, etc., are not as a rule especially altered, and the ossification of the skeleton seems to be punctual and complete. The genital development and that of the secondary sexual characteristics, the hair growth and the quantity of the skin, may all be normal.

The so-called infantile dwarf, on the other hand, is born with a normal weight and height, but backwardness in development manifests itself later on, usually in the earliest years of life. The proportions of the body as it grows are childish throughout, and continue so even in adult life. Bone-development is delayed, and the cartilaginous sutures remain open for an abnormally long time. Similarly the genital development is incomplete and inhibited, but may become normal in later years.

Mentally, both primordial and infantile dwarfs may be quite normal for their age. I knew one of the latter class who was an especially gifted youngster and of excellent disposition. At eleven years of age he was just under 3 ft. 11 ins. in height and his metabolism was quite normal, in that it was equal to that of a normal child of the same weight and size. The viscosity and protein concentration of the serum and the blood picture were normal.

The fat deposit of the infantile dwarf is often poorly

developed, but the condition of the skin and hair is not unhealthy.

Finally, the physiological soundness of these dwarfs is indicated by the well-known fact that there are races and families which combine small proportions with perfect health and normal development. An example is furnished by certain Mongolian races, such as the Laplanders of Norway ; by the pygmies of Central Africa and the Bushmen of South Africa, who measure on an average 4 ft. 3 ins. to 5 ft. in height (H. Zondek).

DISEASES OF THE ADRENALS

Anatomy and Physiology. — The adrenals are a pair of organs set like a cap upon the upper pole of each kidney. Each consists of two parts, distinct in morphology, evolution and function : the cortex and the medulla. The tough substance of the cortex is built chiefly of epithelial cells, containing many nuclei of a lipoid character which break up polarized light. The medulla, which only composes a fifth or a sixth of the section, is soft and contains many nerve-fibres and ganglion cells, especially a peculiar kind of cell-nest, the large polygonal cells which stain brown with chromic acid (chromaffin cells).

The close connection of the adrenals with the vegetative nervous system is recognizable by the presence of numerous nerve-fibres from the semilunar ganglion, the renal and adrenal plexus, and the splanchnic, vagus and phrenic nerves. The secretory fibres are said to pass to the splanchnic nerve. Chromaffin cells identical with those of the medulla are scattered all over the organism, partly in cell-clusters—paraganglia—visible to the naked eye, and partly microscopical. Some of the former are situated, for example, in front of the aorta, down to its bifurcation ; others lie in all the great sympathetic ganglia of the abdomen, on the ganglion of the funiculus marginalis, and so on. The microscopic chromaffin cell-clusters are found wherever there are sympathetic ganglia and nerves. Because of this it is customary to speak of a chromaffin or adrenal *system*.

In addition to these structures, which consist entirely of chromaffin cells, there exist quite often accessory adrenals, made up of both cortical and medullary substance and situated in the abdominal cavity. They sometimes become hyperplastic and take on the work of the adrenals when these are diseased. The function of the adrenal cortex is indubitably a manifold one, but it has by no means been elucidated, and experiments on warm-blooded animals have given very diverse results. It is certain

that the cortex and medulla work in close connection, but the nature of the connection is obscure. Disease of the cortex by itself in man sometimes brings about the full picture of Addison's disease, but sometimes only debility, cachexia, hypotension or hyperpigmentation. In growing persons the adrenal cortex influences in some way not only the muscular tone and strength and the fat metabolism, but also the sex glands and the whole development of the body. Tumours of the cortex can bring about precocious puberty, or in elderly women a peculiar kind of " virilism ".

The most important function of the adrenal medulla is the production of a specific hormone, adrenalin, a derivative of pyrocatechin, the chemical composition of which is well known. (The synthetically manufactured hormone is called suprarenin.) Adrenalin is excreted whenever the splanchnic nerve is stimulated, and exerts its chief effect upon the sympathetic system and the organs which it innervates. It raises the blood-pressure by constricting the arteries, except the coronary vessels of the heart, which it dilates. The capillaries also seem to constrict under adrenalin. The heart-beat is accelerated, contraction is induced in the plain muscle of the uterus, stomach and intestine, and in the contractile elements of the spleen, as has recently been established in man. The musculature of the bronchi dilates under adrenalin, as does that of the pupils ; the dilator pupillæ is stimulated (Loewe's phenomenon). The peripheral muscles are also affected (adrenalin tremor). Adrenalin also apparently exerts a constricting effect on the bladder, and induces in the blood an increase of erythrocytes, and also especially of lymphocytes. The secretion of the digestive glands and kidneys and the respiratory metabolism are also enhanced by adrenalin. An effect particularly worth noticing is the mobilisation of glycogen from the liver and the consequent rise in blood-sugar, and sometimes the excretion of sugar in the urine. This property marks adrenalin out as a vigorous antagonist of insulin, the secretion of the pancreas. The relation between the adrenalin system and the thyroids is probably one of mutual stimulation ; in the hyperthyroses adrenalin is seen to produce an increase of the sensitivity of the sympathetic and its organs to the thyroid hormone. Between the adrenals and the thymus, on the other hand, there is an antagonism.

Addison's Disease

This disease, first described by the English physician Addison in 1855, represents the commonest of the disturbances caused by the destruction of the adrenal function. Its ætiology is not uniform, but the clinical picture is nearly always much the same, even when the origin is different. It chiefly affects men, less often middle-aged women ; among children and the aged it is exceptional. The oldest recorded patient was a man of eighty and the youngest a child of three (Neisser). Since tuberculosis is the most fruitful underlying cause, Addison's disease is often found in persons with a tuberculous history (pleurisy, bone and joint disease or genito-urinary tuberculosis), but rarely in patients with manifest pulmonary phthisis. On the whole, patients with Addison's disease do not as a rule suffer from active and clinically prominent tuberculous processes. In quite a number of cases there is no history of any disease that could account for the condition. Certain authorities have tried to incriminate status thymo-lymphaticus or hypoplasticus as important predisposing constitutional factors, but it is certain that they are only present in some of the cases. The course is as a rule chronic. It may occasionally run on with exacerbations and remissions for many years : I know one case of over ten years' standing. An acute onset and course are rare.

Symptoms and Course.—The insidious onset first manifests itself in general distress, especially an increase of *muscular fatiguability* and loss of energy, which often contrast noticeably with the robust volume of the muscles and fat, and which may gradually become very marked without the occurrence of any genuine paralyses. The disease is sometimes accompanied by dragging rheumatic pains. Severe pains in the back are very common. The nervous and psychic counterpart of the muscular fatiguability does not at first appear, but usually shows itself later on ; many patients suffer from headaches, vertigo, a tendency to fainting, a complete loss of energy, somnolence, and a diminution

of mental capacity. In others, however, these psychic functions—in strong contrast to the muscular debility—remain unimpaired to the end.

As a rule patients gradually become *emaciated*, but not extremely so. True cachexia and complete loss of fat, as in phthisis and carcinoma, do not usually occur. The same holds good of the *blood picture* ;. patients practically always become pallid by degrees, but the blood hardly ever shows any diminution in the number of erythrocytes or the quantity of hæmoglobin. There is generally a low grade of secondary anæmia, and I have found polycythæmia in one or two cases. The leucocyte count is usually normal, but there is often a marked lymphocytosis. The serum-bilirubin is not increased, and the other physical and chemical properties of the blood are also normal, with the exception of the blood-sugar. This, on account of the absence or diminution of the adrenalin secretion, is very scanty and only shows a minimal rise when adrenalin is injected. I have found fasting values of under 0·05 per cent.

Gastro-intestinal disorders, loss of appetite, feelings of fullness, malaise, hiccough, pressure and pain in the stomach occur very early and constantly. Later there is copious vomiting. These are often the first symptoms for which the patient seeks advice. Externally there is nothing wrong with the stomach, and there is no striking change in its appearance or function under X-rays. The secretion is, however, practically always impaired ; it is the regular thing to find an absence of free hydrochloric acid and a very reduced total acidity. Achylia occurs, and lactic acid and blood are absent. The intestinal disturbance usually takes the form of constipation, but profuse diarrhœa and sometimes fatty stools are often seen in the later stages.

Cardiac troubles are rare. Objectively there is nothing to be seen ; the outline is normal and the sounds usually soft and clear. In the X-ray picture I have on some occasions been struck by the lack of vigour in the heart's action, and H. Zondek described patients with marked cardiac hypoplasia. The pulse is usually somewhat accelerated, regular, and strikingly small and weak. The systolic blood-pressure

is much lowered ; it is nearly always under 100 and often between 80 and 70 mm. of mercury. The diastolic pressure is often impossible to ascertain with certainty. This hypotension, which is indubitably a result of adrenalin deficiency, is quite pathognomonic of Addison's disease, and no case should ever be diagnosed as typical in its absence.

This does not altogether apply to the skin change, the *hyperpigmentation* from which the condition was originally called the " bronze disease ". In typical cases the pigmentation of the skin and mucosæ runs parallel to the other symptoms. It begins on the sites of predilection, where the pigment is plentiful, such as the nipples, external genitalia, axillæ, backs of the hands and the face, and also appears at an early stage on the edges of the lips, and in patches on the buccal mucosa, especially the inside of the cheeks and the hard palate. Sometimes it appears in patches on the conjunctiva. Later on the bronze discoloration is diffused over the whole body, finally giving the patient a definite negroid or Malayan colouring. Not a few patients, however, even of those who eventually die, escape this general pigmentation, and are merely bronzed on the genitalia, nipples, armpits, face and mucosæ. Some fatal cases indeed only develop a very slight brown tint, but they hardly ever fail to show patchy pigmentation on the borders of the lips and the buccal mucosa.

Very occasionally indeed Addison's disease has been observed without any pigmentation at all. From the outset there is a very conspicuous tendency to an abnormally rapid and intense tanning under sunlight, which in fact may be the first symptom of the morbid displacement of pigment and may precede the subjective disease by some years. Another striking peculiarity is the extra pigmentation of those parts which bear the pressure of the clothing. A darkening of the head and scalp-hair has sometimes been observed. Occasionally there are found enlargements of the spleen and lymphatic glands. The liver, in cases without amyloid disease, is unaltered, and the genitalia remain structurally intact but undergo impairments of function manifested in amenorrhœa, frigidity and impotence. In a few cases I have

seen a rather sluggish, symmetrical ankylosis of the large joints, especially of the hip. The kidneys are very rarely involved, and albuminuria and glycosuria are usually absent. In many cases, however, disorder of the water excretion and power of renal concentration have been observed. Sometimes there is an increase of indican, urobilin and urobilinogen.

The *low temperature* of the patients, even those whose underlying conditions (such as tuberculosis) incline them to fever, has always been a conspicuous thing. I have seen it remain below 96·8° F.

Except for the debility, somnolence and depression, the nervous system shows no typical signs of disorder.

The *metabolism* is not as a rule subject to any marked changes. Emaciated patients can be kept in a state of nitrogen-equilibrium on a diet of low protein and calorie content. When diarrhœa is absent, nitrogen and fat are well used up (H. Zondek). Urea, uric acid and ammonia are excreted in normal quantities (Kolisch and Freund). The abnormal lack of sensitivity of the low blood-sugar level to adrenalin corresponds with the adrenalin poverty of the patient. I have once found the respiratory basal metabolism appreciably lowered (by 15-20 per cent) and the specific dynamic protein action diminished ; this agrees with the findings of other authors.

The course is, as we have said, chronic, either slow and regular, or progressing in spurts and remissions. If the underlying disease of the other organs—carcinoma or tuberculosis, for instance—does not kill the patient, Addison's disease leads in the end to an extreme exhaustion with gastric symptoms, especially vomiting ; severe peritoneal symptoms (pseudo-peritonitis, according to Ortner) in the foreground, and occasionally a hæmorrhagic diathesis. The final stage is often a condition of coma, sometimes with delirium and epileptiform convulsions. It is to be noted that Addison patients who may not have seemed very ill may succumb very rapidly to relatively trivial complaints. I saw a patient die from a quite mild acute nephritis, and another after an attack of male-fern poisoning which was

not in itself at all severe. Other authors have lost patients after acute exertion.

Ætiology.—By far the most frequent cause is a bilateral —hardly ever a unilateral—tuberculosis of the adrenals. Decidedly less common are bilateral carcinoma or sarcoma, metastatic more often than primary. Other conditions, such as adenomata, gummata, hydatids and hæmatomata, have been observed. Simple atrophy, with or without advanced inflammation, is sometimes the cause, and so probably are hypoplasia and aplasia. Virchow observed a hæmorrhagic inflammation in very acute cases, and Bittorf saw a benignant case of Addison's disease after typhoid.

Anatomically Lewin found demonstrable disease of the adrenals in 88 per cent of cases. In 12 per cent there were no histological changes, but this of course does not exclude a functional disorder. Changes in the local sympathetic nervous system were sometimes absent in these cases. Other patients show gross or merely histological changes in the cœliac ganglion. A feature of the majority is the total, more rarely the partial, caseation of both adrenals. Manifest tuberculous changes in other parts of the body may be lacking, but there is of course nearly always some primary tuberculosis manifest in some other organ. Patients with a unilateral or bilateral metastatic tumour or gumma are much rarer, and amyloid disease of the adrenals with Addison's disease is extremely rare.

H. Zondek answers the question of whether Addison's disease originates in the medulla or the cortex of the gland by the opinion that both parts share in the ætiology. Cases have been known, however, in which the syndrome was caused exclusively by destruction of the cortex and its functions.

The **prognosis** in a typical case is nearly always unfavourable, although it is difficult to estimate the expectation of life. "Cured" cases are usually wrong diagnoses (mild forms of pluriglandular insufficiency, for example). Cases in which the disease is caused by syphilis, tuberculosis, hydatids or typhoid are very rarely known to recover (see below).

Treatment has so far accomplished little or nothing. There is at present no effective substitution therapy, and fresh sheep glands and liquids or solid extracts, whether given by the mouth or subcutaneously or intravenously, have been of no avail. The same is presumably true of the insulin treatment which has been recommended recently, for it exerts no reliable effects even on the symptoms. In spite of the successful transplantation of a healthy adrenal gland from a young epileptic, a patient of mine died very soon, and an effective organotherapy is still to be discovered. In one case the symptoms of Addison's disease disappeared after the extirpation of a hydatid, and recovery has been recorded in one or two syphilitic patients after specific treatment. Very occasionally a cure has resulted from the extirpation of the infected gland in unilateral tuberculosis, and Bittorf saw a case which recovered spontaneously from Addison's disease caused by typhoid.

There is therefore hardly ever anything to be done except to treat the pains in the abdomen, limbs and back and the achlorhydria, vomiting and diarrhœa. Drastic purgatives, which may lead to intractable diarrhœa, should be avoided. The psychological treatment of the subjective depression, which is usually severe, is important but difficult.

The **diagnosis** of advanced cases does not, as we have observed, present much difficulty if the syndrome of hyperpigmentation, hypotension, debility, achlorhydria with vomiting, and progressive decline is present. It is necessary, however, to eliminate a number of diseases which have melanodermia as a symptom. The chief of these is Biermer's anæmia, the blood-picture of which soon determines the diagnosis. The same applies to lympho-granuloma, bronzed diabetes (in which there is a rise in the blood- and urine-sugar-content and a cirrhosis of the liver) and other diseases of the hepato-splenic system associated with hyperpigmentation, such as Laënnec's cirrhosis, Banti's and Gaucher's diseases, and so on.

Pigmentation is not uncommon in Graves' disease, and is often seen in diffuse forms of sclerodermia. Adrenal insufficiency has often been observed as one symptom of a pluri-

glandular insufficiency or an endocrine sclerosis, but the pronounced pluriglandular character of the syndrome will make diagnosis easy. The same is true of the dystrophia pigmentosa of E. Leschke, a pluriglandular insufficiency of endogenous origin with the symptoms of Recklinghausen's disease. General melanosis has been seen in malaria, scurvy, and the final stages of pellagra, but the underlying cause is fairly easy to establish in each of these. Melanotic sarcoma, which also sometimes leads to a general browning of the skin, should be recognized without difficulty from the presence of the tumours. Arsenical melanosis may be identified from the history and from chemical investigation. Tramps' melanodermia, caused by prolonged infestation by lice, is likewise unmistakeable.

There exist, however, cases of general melanosis, especially pulmonary tuberculosis and carcinoma, in which the diagnosis must remain open. It is self-evident that the physiological hyperpigmentation of many individuals and races may give the diagnosis a certain difficulty, but it has nevertheless been correctly made on Hindus, mulattos and Arabs.

Rare, atypical forms are seen. F. Boenheim, Croom and others have recently described the clinical picture of a mild chronic adrenal insufficiency which occurs sporadically and in families, and which does not seem to shorten life. The syndrome is characterized by slight pigmentation, associated with great exhaustion, nervous sensitivity, muscular weakness, headache, gastric disorders (hyperacidity), low blood-pressure, a tendency to diarrhœa, a diminished genital function, and lymphocytosis. Adrenalin tablets seem to have been of some value. Until post-mortem findings are available, a diagnosis of mild adrenal deficiency should always be regarded rather sceptically. In any event, the separation of these cases from constitutional asthenia with hypotension is bound to be difficult and based in some measure on subjective symptoms. It is equally hard to draw the line between Boenheim's picture and chronic mild pluriglandular insufficiency or Simmonds' equally hypothetical syndrome

of mild pituitary cachexia or other similar conditions. Nevertheless, the attempt should be made to differentiate between these syndromes, if only on organotherapeutic grounds.

Acute cases of Addison's disease are rare. An example is the extremely rare adrenal apoplexy, which shows itself in severe peritoneal symptoms, diarrhœa, fall in blood-pressure, etc., and is very rapidly fatal. Pigmentation does not usually occur, as there is not time for it to develop. Patients have died very quickly from bilateral adrenal infarct caused by embolism, and also from a mysterious rapid atrophy of the adrenals, as a case showed me not long ago. An adequate history, however, shows pretty clearly that the patient in these " acute Addison " cases has been more or less ill for some time with general symptoms, even if no marked pigmentation has been present, and it is therefore as well not to be too ready with the diagnosis of acute Addison's disease. J. Bauer described a very noteworthy form with the symptoms of intermittent muscular debility, low blood-pressure and hypoglycæmia, but no pigmentation ; autopsy revealed amyloid disease of the adrenal cortex alone. On the other hand, cases have also been described which showed very intense pigmentation but no debility or hypotonia.

Diseases due to Excessive Activity of the Adrenal System

In contrast to Addison's disease there are conditions of excessive adrenal function, some of which are very doubtful and the subject of much controversy, while others are extremely rare.

The literature of tumours of the adrenal cortex and other parts of the chromaffin system (*e.g.* the paraganglia) is so scanty that it is almost impossible to formulate a symptomatology for these cases. Rise in blood-pressure, spasms, tachycardia and severe vegetative-nervous crises seem to play the principal part. The much-debated question of

whether the rise in blood-pressure due to nephritis and that of essential hypertonia are based upon an excess of adrenalin can be answered to-day by a definite negative. Nor, probably, does the chromaffin system and an excess of its function play the part in the production of arteriosclerosis in man that was ascribed to it on the basis of experiments on dogs, in which adrenalin produced a disease of the aortic media, but one quite unlike any known human condition.

Tumours of the adrenal cortex, it should be noted, do not cause any regular endocrine symptoms. This applies especially to those commonest of all hypernephromata, the Grawitz tumours, which only in the rarest instances exert any effect on the blood-pressure, the pigment distribution, or the genital function and structure. Much more characteristic are the symptoms of tumours, usually adenomata, associated with manifest hyperfunction of the adrenal cortex. They lead in children to precocious puberty and premature bodily and mental growth, and in sexually-adult persons, especially women, to a peculiar virilism or hirsutism (*q.v.*).

DISORDERS OF THE GONADS

By Dr. Franz Prange, Rostock i. M.

Anatomy and Physiology.—The male and female gonads belong to the type of endocrine glands which have a double secretion, an internal and an external; the latter is concerned in the genesis of reproductive cells (ova and spermatozoa) and has a significance wider than that of the individual, since it bears on the preservation of the race. The former discharges into the blood-stream a secretion specific for sex, which gives the individual his or her sexual characteristics. Virchow has expressed this fact in his well-known formula: "Propter solum ovarium mulier est quod est".

The gonad is the only endocrine gland that undergoes considerable change of position in the course of its development. Originating as an outgrowth of the cœlomic epithelium, in which the primordial sex cells wander, it is extruded by the gubernaculum into its final place: as a testicle into the scrotum, and as an ovary into the pelvis. Disturbances may occur in the course of this migration: the testicle may stay in the abdominal cavity half-way down and the scrotum remain empty (cryptorchism), or the ovary may in rare cases reach the labium majus (pseudohermaphroditism).

The male gonad consists of tubular, reproductive and interstitial tissue, the last of which fills up the intermediate spaces. The seminal canal contains reproductive cells in different stages of their evolution and Sertoli's cells, which perform nutritive functions. In the interstitial tissue there are found, besides numerous connective-tissue elements, the great lipoid-containing Leydig cells, which are especially numerous and succulent at the second quarter of the embryonic period and again about the time of puberty (Kassai, Lipschütz), and so compose at this stage of development the greater mass of the testicle. After puberty they decrease in size and number both relatively and

absolutely, and in the normal sexually mature testicle they are only encountered singly or in groups of two to five. When the parenchyma of the mature testicle is damaged, however, they initiate the process of regeneration of the semen-producing apparatus by an enormous proliferation reminiscent of the appearance at puberty. Steinach, believing that they were actually the secretory elements, described them as the "gland of puberty". In opposition to this view other authorities (von Hansemann, Stieve and others) have ascribed the production of the specific sexual hormone to the intratubular cells, especially those of Sertoli. In grafts with an effective secretory function these are always found together with the Leydig cells, while, when the seminal cells are completely atrophied, the interstitial cells usually disappear as well. Lipschütz claims to have succeeded in isolating the "puberty glands", and Benda also inclines to Steinach's conclusion that the endocrine principle lies in the interstitial part of the testicle only.

The origin of the female secretion is even more debated than that of the male. Here there are a number of anatomical complexities to be considered, such as the corpus luteum, the atresic follicle, and the stroma cells. In the place of the follicle, or when the ovum has died, the first two transform the granulosa cells into large succulent, lutein cells, which attain, especially in the corpus luteum, to very great dimensions. In addition to the granulosa lutein cells, which resemble the cells of Sertoli, the follicle cells of the theca interna also multiply and change into lutein cells. In the later stages they grow in between the granulosa-lutein cells, so that the two cell elements appear to undergo internal fusion. Besides these descendants of the follicle, there also exist in the connective-tissue stroma of the ovary the great plasma-containing cells, which often unite in nests and appear to enclose lipoids, so that many investigators see in them an analogy to the interstitial cells of the testicle.

The secretory action of the gonads is general and also sex-specific. During the period of development the sex hormone has an accelerating action upon the union of the epiphyses of the long bones, so that when it is absent the condition of eunuchoid tallness supervenes in both sexes. The sex-specific effect depends in the highest degree upon the plasticity of the organs upon which it acts (the sexual characteristics), and these vary in their capacity for reaction according to the age of the individual. The question has not yet been settled whether the sexual hormone has merely

a protective action (Halban) or a formative one (Herbst) or, in other words, whether the body possesses in all its cell-complexes a weakened but no less an autonomous chromosome-fixed sexual specificity, which only requires the development of an adequate hormonic stimulus, or whether the body is asexual and derives its sexual characteristics exclusively from the hormone. It is certain that the artificial introduction of hormones into individuals before puberty will only intensify homologous sex-characteristics which are already present in the constitution, and that it cannot supply dispositions not already there. It is possible, for instance, by transplantation of the ovaries, to induce lactation in the rudimentary mammæ of the castrated male porpoise, but not in those of the male rat, in which the capacity for mammary function disappears before birth. The success of substitution-therapy is therefore governed by the plasticity of the organs which it affects ; this plasticity is determined by age and has very well-defined boundaries. This is why, in order to influence successfully the sex characteristics of persons with gonadal inadequacy, it is necessary to commence substitution-therapy as early as possible.

The chemical composition of the sexual hormone is unknown ; no one has yet succeeded in isolating it. Nevertheless, there exist organic gonadal extracts which exert a sexually-specific effect, though an attenuated one, upon the organism. Since, however, in many cases—and especially with testicular preparations—the action is merely that of an unspecific stimulus, transplantation still offers the best prospect for severe cases.

Agenitalism

(Castration, Eunuchism)

Complete absence of gonadal function results either from a congenital defect in the sexual glands or from one occurring in early youth or later. Congenital total aplasia is admittedly a rarity ; it appears either as an isolated defect or—much more often—as part of a severe constitutional dysplasia, especially in hereditary diseases such as Friedreich's ataxia, myasthenia, myotonic dystrophy, Erb's dystrophy, and hæmolytic icterus. More frequent is the early loss of the testicles through castration. This operation, as everyone knows, is performed everywhere on many kinds of domestic animals to make them grow fat or to increase their working

capacity. Early castration has been performed on man for various reasons; for instance, upon future harem guards in

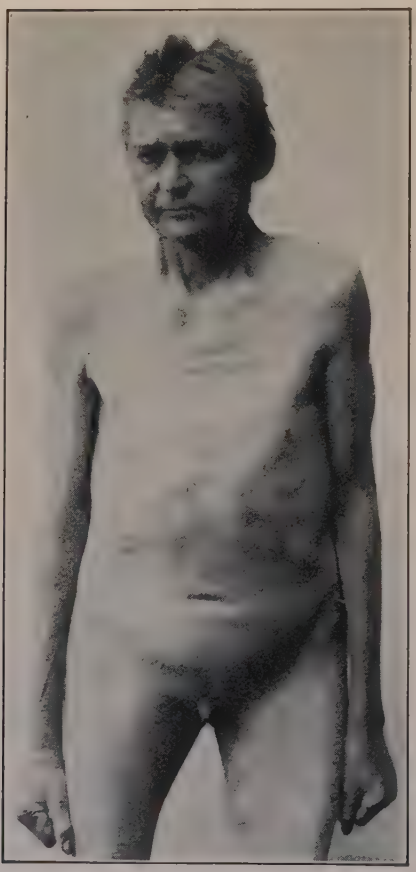


Fig. 35.—A patient of 60. The sexual abnormality is obviously congenital, and there has never been an active sex life. Autopsy revealed a complete atrophy (? aplasia) of both testes, which were only demonstrable as two thickenings about the size of peas. (Grote's case.)

the East and sopranos in the Vatican. It was much practised formerly on ritual grounds (Skopzen)[1], and is performed

[1] Translator's Note.—Skopzen: a Russian semi-secret, semi-religious society, the members of which practised flagellation and mutilation. The women cut off their breasts and the men castrated themselves.

to-day in several American States for eugenic reasons; for instance, on mental patients, epileptics and criminals. The castration of women or female animals on similar grounds is hardly ever performed.

The **symptoms** of agenitalism show themselves, as might be expected, after the castration is complete. When agenitalism occurs soon after birth we find the symptoms which have been made familiar in Oriental eunuchs and Roman soprani. When the testicles are lost, the development of the penis, prostate and seminal vesicles comes to a complete standstill. The subjective and functional sexual life is usually lacking in both sexes; in women menstruation is absent. The secondary sexual characteristics do not develop. No hair grows on the face, but there is no tendency to baldness. The body-hair remains weak and feminine. The larynx remains small and unossified, and the voice high and childish. With practice, typical soprano and alto voices are produced. A noticeable feature of the bony growth is the lateness of fusion of the epiphyses, a factor which leads to eunuchoid tallness. In addition to this the legs are remarkably long; when the patient stands up he looks a giant. The length of the arms is also abnormal. The trunk skeleton usually shows no anomalies. The skull is often relatively small and the bones of the face are neither clear-cut nor prominent, and their shape is somewhat feminine. The pelvis also inclines to the feminine form.

The fat deposit behaves in various ways. In tall eunuchs of either sex it may be normal or even remarkably scanty. Castration obesity, on the other hand, usually affects persons of medium build. Eunuchs and sopranos, even those over 6 ft. tall, are sometimes enormously fat, but very tall castrates, those for instance over 6 ft. 6 ins., generally remain slim.

It should be expressly noted that a few cases of lean, tall "eunuchism" have been observed in women. They, like the men, show a certain approximation to the characteristics of the opposite sex, and have peculiarities of proportion and psychic outlook very similar to those of male eunuchs. Castration obesity is well known; in men it is

localized in the feminine positions of the breasts, buttocks, symphysis pubis, hips and thighs.

Other endocrine disorders commonly associated with agenitalism are hyperplasias of the pituitary and the thymus. An abnormal smallness, and sometimes later an atrophy of the thyroid, has been observed clinically (*e.g.* in eunuchs and Skopzen) and in experimental animals, but hyperplasia has sometimes been seen as well. It is very probable that the development of obesity in agenitalism depends largely upon the functions of the thyroid and pituitary.

The other organs show nothing remarkable. The heart in the lean, tall types is, in my experience, generally small and narrow, sometimes occupying a central position ("drop heart"); [1] the pulse is usually slow and the blood-pressure decreased (hypotonic bradycardia). Postural albuminuria is sometimes noted. There are no organic changes in the nervous system, and the mental outlook in congenital or early agenitalism usually suffers no morbid change. The castrated male, like the castrated animal, lacks the typical manly qualities of adventurousness, boldness, roughness, activity, positiveness and an incisive cast of mind, but hardly ever suffers from psychic defects such as infantilism.

When the gonadal defect occurs in adult life, the results are naturally quite different. In men there is usually an excess of fat with feminine distribution, and often a decrease or absence of facial hair and virile trunk hair. Sometimes the voice becomes high-pitched and a certain amount of involution takes place in the genitalia, the penis and prostate. The potency and the libido, including also that of the inverted sex, are diminished. Sometimes, however, they are apparently retained, and coitus may be performed up to and including ejaculation of prostatic fluid. This is occasionally possible even in cases of early castration. The psyche is only rarely injured; a certain feminine softness has been observed, but the occasional hypochondriacal and depressive reaction to the loss of virility is not specific.

[1] Translator's Note.—There is no English equivalent for this term, *Tropfenherz*; it refers to the drop-shaped, centrally placed hearts seen in asthenic patients with narrow, barrel-shaped chests.

The Climacteric

In females castrated in late life and at the physiological menopause the following changes occur. In addition to the cessation of the menses, which occurs immediately on castration and gradually in the natural change of life, by far the commonest result is an *increase in the fat deposit.* Loss of flesh, plethora, and anomalies of pigmentation occur much more rarely, but a growth of hair on the face is more common, and in addition to this there is a whole host of psychic and vegetative nervous symptoms which may naturally be especially acute and stormy in the artificial menopause, whether surgical or X-ray. The picture differs of course in every patient according to her primitive vegetative and psychic constitution.

The **cause** of the menopausal symptoms lies on the one side in the cessation of the ovarian function, and on the other—perhaps—in the cessation of the monthly blood-loss itself (B. Aschner). Besides the increase in fat deposit, the chief physical symptom is plethora, with a tendency to hæmorrhages of all kinds, for instance, at the nose, gums and genitalia, and hypertonia. The latter, which, according both to B. Aschner and my own results reported by Frau Meier, occurs in one-third of all cases, has indubitably much significance for the general practitioner, both in diagnosis and prognosis. It may decrease when the climacteric disturbances are compensated, but I have seen it persist in many cases and progress to arteriosclerosis and "essential hypertonia", with all their cerebral, cardiac and renal symptoms. Of physical ailments the principal is a tendency to arthritis, myalgia and neuralgia. The post-climacteric, chronic and usually very painful arthritis, beginning in the synovial membrane and capsule, is on the whole the most common form of endogenous chronic polyarthritis. The climacteric neuralgias and polyneuralgias—linked inseparably with myalgias— are an especial affliction to these women. Opinion is divided on the frequency of the incidence of genuine uric acid diatheses after the physiological or

artificial menopause. I think myself that they are very rare.

Some authorities believe in the existence of a chronic hæmoglobin deficiency after the menopause, but I think that this opinion is wrong. Certain disturbances of sight and hearing, which otherwise would occur at the age of involution, have been known to occur prematurely after the artificial menopause. This applies also to the numerous vegetative nervous reactions in the circulatory system, which have been classed as an expression of sympathicotonia due to the removal of the vagotonic influence of the ovary; to the tachycardia, arrhythmia and anginal distress; and above all, to the very constant sudden heat-flushes and other symptoms of vaso-dilatation; tó the hyperidrosis, headache, falling and rapid greying of hair, pruritus, climacteric œdema; more rarely to the angiospastic conditions of the peripheral vessels, and to a great many other symptoms. B. Aschner also mentions a decrease in carbohydrate tolerance, which, however, occurs only very rarely in practice. There is no specific climacteric diabetes. The climacteric is known to bring about a change in certain vegetative neuroses, as, for example, asthma, migraine and idiopathic gastro-intestinal disorders. It sometimes decreases their severity, sometimes, though more rarely, increases it, and sometimes causes a change from one form into another.

The *psychic changes* are exceptionally common and troublesome, and the basic psychical constitution is of course the most important factor in determining them. Depressive conditions, changes of character which show themselves in scandal-mongering, sexual jealousy, coquetry and the like; hysterical, neurasthenic, hypochondriacal and other sentimental and affective reactions, are all frequent manifestations. Gross psychotic conditions, such as, for example, genuine melancholia or a depressive phase of manic-depressive insanity, certainly occur, but are to be ascribed more to the primitive constitution than to the menopause.

Here let me make an urgent appeal to young practitioners not to let themselves give way to the suggestion of lay persons, especially females, who desire to ascribe to the

menopause every kind of condition of which the diagnosis is obscure—from cerebral arteriosclerosis to paralysis and from carcinoma to phthisis.

In addition to these customary sequels of the change of life, it should also be borne in mind that the loss of the ovarian function naturally has an effect upon the structure and activity of the other endocrine organs, usually, however, without a clinically noticeable effect. According to B. Aschner, hyperæmia and enlargement of and lipoid formation in the thyroid, thymus, pituitary, pineal, adrenals, etc., are regular at the menopause, as they are in pregnancy. It has also been mentioned that the opposite may occur and that thyroidal atrophy and myxœdema may sometimes accompany the climacteric.

In describing the **incidence and course** of the artificial and natural menopause it must be repeated that hardly any woman quite escapes more or less pronounced sympathetic, and especially vaso-secretory, disturbances. In only a very few, however, do these disturbances become serious or grossly pathological. This is shown by the very varying duration, which fluctuates between a few months and one or even more decades. The average is one to two years. It is a noticeable fact that young ovarectomized women not infrequently undergo a return of their climacteric symptoms between forty and fifty, when their normal menopause would have taken place. The severity and duration of the symptoms chiefly depend upon the primitive, psychical and physical constitution. It has been maintained that the pyknic type of woman has an easy menopause and the asthenic-ptotic type a hard one, but I do not believe it. There is an axiom—which seems to me a much surer one—and that is that the " sensible ", well-adapted, serious and fully occupied woman practically never suffers from a bad neurosis at the menopause.

Treatment.—Organic preparations such as " Ovaraden ", " Ovariin siccat.", " Oophorin ", " Climacton " and " Folliculin " (B. Zondek) should be tried, but very often they are of no use. It is quite doubtful whether they exert any substitution effect. The usual sedative and antispasmodic

drugs, such as valerian, bromides, nitroglycerine and papaverine, and the hypnotics in ordinary use, are generally necessary. Psychotherapy is important, and the reassuring suggestion that the menopause is a " perfectly harmless condition, but one which every woman must go through once ". Treatment of sequelæ such as arthritis, the neuralgias, adiposity and the thyroses should follow the rules which apply to these conditions. A piece of advice which I do not think superfluous is : be extremely careful, both during and after the climacteric, in treating goitrous patients with iodine, for their condition is especially liable to develop into Graves' disease.

The Male Climacteric

Many authors recognize a climacteric in men beginning at about fifty and showing itself in nervous disorders of vegetative and psychic origin, hypertonia, obesity and changes in potency. The libido, although sometimes raised, is said to be usually diminished, and sexual vigour is said to slacken or disappear. In the absence of an objective menstrual phenomenon in the male, these opinions are venturesome and highly doubtful. To distinguish all these symptoms on the one hand from true neurasthenia and hypochondria, and on the other from incipient sclerosis, is always difficult and usually only possible on subjective evidence. It is certain that the diagnosis of male climacteric is often an euphemism coined to avoid that of arteriosclerosis. Nevertheless, the possibility of a change of life in the man should not be rejected altogether, and an organic preparation such as " Testogan " or " Spermin " may be given experimentally.

Hypogenitalism. Eunuchoidism

The physical and psychic states to which this term is applied take many different forms and arise from various causes. The condition originally called eunuchoidism by Tandler and Gross is the congenital state in the male which is always associated with a certain degree of hypoplasia of the testes.

Symptoms.—Cryptorchism and *hypoplasia* of the prostate, penis and seminal vesicles are usual. The *secondary sexual*

characteristics develop poorly; the facial hair is weak or absent, the body-hair is scanty and feminine, and the voice remains infantile. The most impressive of the external symptoms, however, is the eunuchoid *height*, which reaches 6 ft. 6 ins. or a little over, and the enormous length of the legs and of the arms compared with that of the trunk, which, though often asthenic, is usually normal. The head and face are small. There is no tendency to obesity; on the contrary, nutrition is very poor, and thinness is the rule.

Fig. 36.—Partial eunuchoidism with gigantism (6 ft. 7 ins.) in a man of 32 with morphologically normal genitalia and a fairly good growth of facial hair, but with a soprano voice, complete frigidity and psychic infantilism. (Author's case.)

Types.—The lean, tall type is by far the commonest in men with primary aplasia of the testicles. In women it is very much rarer as an expression of genital hypoplasia or aplasia. I know of only one case. The physical characteristics are much the same as those of male patients. There is nothing very abnormal about the other physical changes. The condition of the internal organs often corresponds to that of the asthenic habitus; there is "drop-heart", hypoplasia of the aorta, weak pulse, hypotension, and ptosis of the abdominal viscera. Morphologically, physiologically and chemically the blood shows nothing out of the ordinary, and the respiratory and other metabolism is normal. Gross disturbances of the other endocrine organs, even of the pituitary, are absent, but hyperplasia of the thymus is said to occur sometimes. Occasionally the mental outlook is infantile, with grave impairment of intelligence and feeling tone, but

the prevalent feature is usually a slight feebleness of mind with a tendency to femininity. When the testes are lost in later life through disease the resulting picture is one of a modified late eunuchism.

In addition to complete cases there are incomplete ones in which, although the genitalia and face- and body-hair are morphologically normal, the patient is absolutely frigid. The other signs of eunuchoidism, such as great height, a high voice and mental infantilism, may be present in these cases as well.

Fig. 37.—Eunuchoidism in a female of 26 with gigantism and leanness. (Author's case.)

There are various forms of these incomplete cases with dissociated eunuchoid disorders. If all tall people were investigated from this point of view, eunuchoid disorders would probably be found more common than is generally believed.

Adipose eunuchoidism or hypogenitalism, in the absence of pituitary lesions, is very rare in men but very frequent in women. The typical patient is a constitutionally fat woman who is either sterile or has become so after having one child. The external genitalia are apparently normal, except that the mammary glands are poorly developed, but the internal genitalia are more or less hypoplastic. Menstruation begins late and continues irregular, or, if regular, it is very scanty and the menopause comes early. Dysmenorrhœa often occurs, and many patients have permanent amenorrhœa. Most of them are frigid, but I have seen patients in this group with normal and even strong sexual desire. The growth of hair may be scant, and on the body it may be weak and

virile in distribution; hair may grow on the face. There is nothing worthy of note in the internal organs. Pituitary changes are never seen. The metabolism, including the respiratory, and the specific dynamic protein action, are normal, and the blood shows nothing unusual.

As has been pointed out, there is also a spontaneous type of late eunuchoidism associated with obesity. It consists of women who before the first or second pregnancy have been markedly adipose and had scanty periods, and who after it undergo a premature menopause and involution of the genitals.

Fig. 38.—Eunuchoid tallness. (Grote's case.)

Signs of psychic infantilism are seldom seen in this obese type of hypogenitalism in women, but psycho neurotic disturbances of all kinds are frequent; these are sometimes true constitutional products and sometimes the results of physical and psychical experience, such as disillusionment and lack of sexual harmony.

In **differential diagnosis** it is necessary to differentiate as sharply as possible the tall and fat hypogenital eunuchoid patients who have just been described from those whose condition is referable to the thyroid and, more still, to the pituitary. We have seen that all forms of hypothyroidism lead to secondary hypogenitalism. Thyroaplasia and hypoplasia with juvenile myxœdema and endemic cretinism inhibit the development of the genitalia to a greater or lesser degree, generally altogether.

The myxœdema which occurs spontaneously or as a result of the extirpation of the thyroid paralyses the sexual life of either sex, and leads in women to a premature involution and menopause.

True adult acromegaly produces the same result, and visible and functional hypogenitalism, generally secondary, is also the rule in pituitary gigantism with or without marked acromegaly. It is more pronounced still in the adipose form of pituitary disorder, dystrophia adiposo-genitalis, in which cryptorchism and aplasia of the testes are often observed. The presence of marked local pituitary symptoms will usually facilitate diagnosis; they do not occur in Biedl's cerebral obesity, which may usually be distinguished from primary hypogenital obesity by the symptoms, often familial, of mental disorder, familial syndactyly, inflammation of the choroid and retina, pyrgocephaly, etc. The pituitary cases have a normal basal metabolic rate with very little or no specific dynamic protein action (Kestner, Plaut, Liebesny).

Many forms of pluriglandular insufficiency include hypogenitalism; for example, morbid pre-senile involution. Syndromes in which the pluriglandular symptoms are only accessory and not causal, such as myotonic dystrophy, sclerodermic dystrophy, hæmolytic icterus, Recklinghausen's disease, and others, often show congenital or acquired hypogenitalism. Many diseases, moreover, run their course with a greater or lesser degree of manifest hypogenitalism.

It is important on therapeutic grounds to distinguish between these conditions. Hypogenitalism calls for extract of the male or female gonad (even though neither exerts a very constant effect). Much publicity has been given to the homoioplastic graft, but the permanence of its results is very doubtful. On the other hand, pituitary cases, as we have seen, are always suitable for local treatment by surgery or X-rays. In the other forms of hypogenitalism, which vary so much in their ætiology, treatment should be directed towards the underlying cause.

SEXUAL INVERSION

By Dr. F. Prange.

We understand nowadays by this term the appearance in an individual of sexual characteristics which are not

appropriate to his or her primary sexual constitution. It therefore includes all the very extensive territory bounded on the one side by physical hermaphroditism and on the other by sexual aberrations of purely psychic origin. In diagnosing sexual inversion we must be especially careful not to confuse the sexual characteristics of simple hypoplasia with heterosexuality. The obese eunuchoid patient often puts on huge quantities of fat in the region of the hips

Fig. 39.—An extremely effeminate youth of 20. Tendency to affect dress of the opposite sex (transvestitism); auto-erotism. (Dr. Prange's case. Institute of Sexual Science, Berlin.)

and breasts, and the mistake is often made of supposing that this denotes a change towards the feminine type, although no mammary gland tissue is present. Similarly, the psychical inactivity, emotional flaccidity, liability and indifference of eunuchoids and castrates is sometimes mistaken for feminism. The essence of inversion does not lie in the patients' own sexual characteristics, which are generally poorly developed, but in the presence of characteristics of the opposite sex. Nowadays the appearance of one charac-

teristic only, physiological or psychological, of the opposite sex in a personality with an otherwise harmonious sexual life is not in practice taken to indicate a state of inversion. Thus a sturdy growth of hair on a woman's chest or upper lip or a weak growth there in a man ; the adoption by a woman of the professions of surgery, law or engineering, or by a man of those of dress-designing, hair-dressing or art, do not in themselves constitute evidence of inversion. It is necessary in such cases to look for further signs of the same kind, and more especially to see how far the psychic urge and instincts are directed towards adequate sexual aims. It is also of great importance to know how the particular individual behaved in childhood—whether, for instance, he or she played at manly or girlish games—and to trace the development of puberty. Endocrine imbalance at this period is probably present if the boy's voice breaks late and hair is slow to appear on his face, and if the girl's menstruation is delayed and she is late in acquiring the curved feminine contours. Defects of this kind should of course lead to an examination of the external and internal genitalia, especially for cryptorchism, hypospadias or epispadias, hypertrophy of the clitoris, hypoplasia of the uterus, and vaginal atresia.

Fig. 40.—A virile, homosexual woman of 25. Uses a male Christian name and wears men's dress. (Dr. Prange's case. Institute of Sexual Sciences, Berlin.)

It is then necessary to pay careful attention to the psycho-physical factors. Some border-line cases may be very difficult, and a prolonged survey of the whole process of development is necessary before an unequivocal diagnosis can be made. It is also very important to consider race and environment. A vigorous growth of hair on a Southern woman and a similar growth on a light northern blonde must be allowed very different evidential value, and the

homosexual tendencies of a boarding-school boy at puberty or of an æsthetic young man living in a large town and crammed with psycho-analytic literature have a different significance from those of a Pomeranian peasant.

It follows, therefore, that a **diagnosis** of sexual inversion cannot usually be made at first sight. On the contrary, when, for example, the patient has not reached puberty, it may require a year's observation, and demand of the physician not only an eye trained by long use to detect fine shades of constitutional pathology, but also a knowledge of and an insight into morbid psychiatry. Most cases of inversion which come to the notice of the general physician, house physician or neurologist for some more or less obscure organic nervous complaint or psycho-neurosis do not belong to the museum of curiosities called teratological hermaphroditism. They constitute a class of psycho-physical borderline cases, and only a very thorough weighing of individual stigmata, combined with intuition based on experience, can correctly estimate their personalities and—what is more important and the last test of medical skill—give them a new synthesis and a new place in the community. Their subjective difficulties can usually be relieved, and they can be helped to adapt by psychological treatment and organotherapy.

Fig. 41.—A virile woman of 33, with pronounced leanings towards masculine dress. No menses for five years. The whole genital track is distinctly hypoplastic. Strong growth of hair in axillæ and on lower legs. (Dr. Prange's case. Institute of Sexual Science, Berlin.)

Note.—We shall now discuss hermaphroditism and homosexuality as the two most important expressions of the constitutional anomaly known as inversion. The small size of this volume does not allow us to do more than mention other important disturbances of the sexual function such as ejaculatio præcox, frigidity, fetishism, psycho-sexual infantilism and transvestitism, all of which we are inclined to regard as expressions of a pathological inversion of the sexual constitution dependent upon faulty endocrine function. Considering that even massive works on endocrine pathology, such as those of Falta and others, do not attempt to cover this branch of the subject, the reader would hardly expect to find it fully treated in this book.

HERMAPHRODITISM

By Dr. F. Prange.

When we apply the term " hermaphroditism " to certain cases which exhibit a more or less comprehensive picture of heterosexual organic development, we do it more on historical and practical than on ætiological and clinical grounds. In company with other authors, therefore, we will not attempt to draw a line between " true " hermaphroditism and " pseudohermaphroditism " and will simply look upon these forms as different grades of a constitutional sex inversion, just as there may be in the purely psychological hermaphroditism of homosexuality. The key to the understanding of these constitutional anomalies must be sought in the bisexual potentialities of the developing organism (Waldeyer, Plate). The manifestation of hetero-sexual characteristics, on the other hand, depends upon a prevalence of one of the two sex enzymes, introduced into the fertilized ovum by the parent ovum and spermatozoon respectively (Goldschmidt), but this enzyme is nevertheless not identical with the gonadal hormone. The appearance of heterosexualism is therefore conditioned by the chromosomes (cf. the experiments of Goldschmidt upon interchange of sex in butterflies, those of Hertwig upon the same phenomenon in frogs, the zygotic interchange of sex in twin goat kids performed by Prange, and the existence of stocks of human hermaphrodites (von Neugebauer, Hirschfeld, Poll). Their characteristics, which

vary in the strength of their definition, depend on the protective effect of the sex-specific gonadal hormone. Only in this way is it possible to explain the great variety of forms in which hermaphroditism displays itself ; at one end of the scale are the very rare cases which have both testes and ovaries (Pick, Salén), and at the other are cases in which the gonad merely possesses an opposite character to the apparent sex of the individual, or a more or less developed uterus is found in association with male external genitalia. In all these doubtful cases, which usually also possess a medico-legal significance, mostly connected with alterations in the Registrar's books, the first thing to consider is the patient's subjective feelings as to which sex he belongs to. These are sometimes quite definite, but they are equally often ambiguous. The next step is to inquire into the direction of the sexual inclinations and into the nature of the excretory products—menstrual blood, semen, etc. We had a patient with morphologically an all-but-normal female appearance who came under observation for homosexuality and general psychic virilism ; the substance secreted on orgasm was found to contain living spermatozoa. It is important, moreover, to establish whether the hetero-sexual characteristics were present at birth and developed further at puberty, or whether they appeared suddenly in later life. This is especially important in the diagnosis from new growths which may bring about a change of sex, such as teratomata of the testes, ovaries, adrenal cortex, or even the pituitary

Fig. 42.—External genitalia with hypertrophic clitoris in a spinster of 36 with a masculine distribution of hair and aplasia of the mammæ, but with normally developed internal genitalia. (Author's case, from the Rostock University Medical Clinic.)

(*q.v.*), appearing especially in the fourth or fifth decade. These call for immediate surgical intervention because of their malignity (Sellheim). A thorough inspection of all the sexual characteristics, such as the distribution of hair ; pitch of voice ; relation of the length of the trunk to that of the limbs, particularly an abnormal length of leg ; fat distribution ; mammary development ; date of maturity and direction of the inclinations, together with a search for disorders of other endocrine glands, is therefore always indispensable.

Before undertaking surgical intervention the adviser should consider very carefully in what direction he proposes to proceed. Several unfortunate results have shown that in extirpating heterologous and implanting homologous gonads it is not the characteristics of the external genitalia that matter so much as the basic tendencies of the psychical and physical personality. In dealing, therefore, with difficult questions of this kind in cases which, because of the immense number of possible combinations of constitutional peculiarities, are always unique, the decisive word should always be reserved for an experienced specialist. In milder cases, which usually sail under the colours of sterility, frigidity and dysmenorrhœa, the diagnosis should first be confirmed, and other anomalies of internal secretion, such as infantilism, should be eliminated. A substitution-treatment with the appropriate gonadal extract will then often be found effective, while the predominant psychical inversion may be treated by psychotherapy.

HOMOSEXUALITY

By Dr. F. Prange

This disease picture was looked upon until recently as the peculiar domain of the psychiatrist and the medico-legal expert. The term implies the sexual predilection for persons of the same sex, usually with a corresponding aversion from and impotence towards the opposite sex. Although von Krafft-Ebing still regards homosexuality as a purely psychical phenomenon, the classical experiments of Harms, Sand and

Steinach, who succeeded in changing the sex of animals by implantation of glands of the opposite sex, have revealed it as a variant of the biological constitution (Hirschfeld). In the light of this broader conception, some authorities have suggested that even human homosexuality may be largely due to the presence of a hybrid gonad or gland of puberty. The view that a fault in the function of the sexual hormone, buried deep in the constitutional make-up, actually plays a causal part in a great many cases of homosexuality, is supported by the fact that close investigation will usually demonstrate other hetero-sexual stigmata as well. These may be, in men, a high voice ; signs of abnormal development of the breasts ; poor growth of facial hair ; a feminine proportioning of the pelvic width to that of the hips, and a feminine fat-distribution, besides psychical feminism such as the affectation of feminine attire and a tendency to womanly occupations. In women they may take the form of a gruff voice ; a strong growth of hair, especially on the linea alba ; paucity of mammary tissue, breadth of shoulders ; vigorous muscular development, a scanty fat-deposit, and an inclination towards masculine occupations and dress. One characteristic of endogenous sexual inversion is that first observed by Weill. In the sexually normal person the relation of the length of the trunk to that of the lower limbs is as 100 : 94 ; in eunuchoids it is as 100 : 125 ; and in homosexual persons of both sexes it is as 100 : 105. In my experience this sign, which I have myself observed in 75 patients, is usually present also in other forms of psycho-sexual aberration such as exhibitionism, psycho-sexual infantilism and auto-eroticism, and may depend upon an insufficiency of the gonadal hormone which may manifest itself very early in life, as it does in the bony extremities of the eunuchoid type.

That homosexuality is determined by hereditary biological factors is further confirmed by Walter Wolf's studies of the genealogy of homosexual persons. In using the term " homosexuality ", which is a purely functional and psychiatrical concept, it is necessary to distinguish most carefully between homosexual practices and homosexual personality. The former may be determined entirely by

environmental conditions (close confinement in an institution, or intoxication, especially by alcohol or cocaine), and are merely expressions of sexual relaxation which appear and disappear without any deep relation to the personality. The homosexual individual, on the other hand, even though he may indulge in no homosexual practices, is a well-defined

Fig. 43.—Two men of 18 of extremely feminine appearance with a tendency to transvestitism. (Dr. Prange's cases. Institute for Sexual Science, Berlin.)

type with an inverted sexual constitution, in whom the homosexual tendency appears as a purely functional symptom. To what extent homosexual tendencies that manifest themselves later in life are the expression of a hitherto latent factor or a psychogenic lesion is usually only ascertainable by a very thorough analysis. Indications of psychological sex inversion before puberty are especially important ;

the significance of sexual dreams, however, is apt to be somewhat overestimated in diagnosis. My own experience has shown that apparently normal persons of all ages are capable of producing markedly homosexual dreams, clearly recognizable as such in spite of the absence of any frank psycho-analytical symbols. In dealing with homosexuality it is necessary to guard against jumping to conclusions; against deducing, for example, a homosexual inclination when a well-established tendency towards transvestitism is the only evidence. About 55 per cent of persons who show hetero-sexual tendencies in their dress are not homosexual at all, even if they also exhibit, as they usually do, a considerable degree of metatropic behaviour, such as the manifestation by a man of a passive and by a woman of an active attitude towards the opposite sex (Hirschfeld).

The treatment inaugurated by Steinach and Ära consists in the extirpation of one or both the genital glands and the implantation of one conforming to the proper sexual inclination. Lichtenstern claims to have actually brought about transformation in this way. The six cases of indubitable endogenous homosexuality which I have observed for some years before and after surgical intervention have not shown the slightest signs of improvement, even though one —a young doctor—has had two new sets of testicles.

I do not consider it justifiable to regard the hetero-sexual dreams and tendencies which some patients manifested very soon after the operation, and which in no case led to normal coitus, as due to the secretion of hormone; this view is to my mind a wish-fulfilment produced by suggestion. A civilized man is not a guinea-pig whose impulses proceed purely from its vegetative levels. He is an individual with a complicated sexual psychology, in which the predominating elements are cortical and which is inextricably bound up, not only with the spinal centres which govern erection and ejaculation, but with his whole psychical equipment. Steinach claims to have seen Leydig cells, similar in character to the female lutein cells, in the homosexual testicle, but I have never seen them. On the contrary, my investigations revealed many hypoplastic seminal tubules together with

a slightly increased number of interstitial cells, showing a slight impairment of the semen-producing parenchyma with regenerative processes in the interstitium.

Treatment must be chiefly psychical and consist in bringing the existing rudimentary hetero-sexual material up into consciousness and enabling it to be turned to good functional account. Since histological investigation has shown that some degree of testicular insufficiency may be present, a specific organic extract may be of use, apart from its suggestive value. In very extreme cases treatment must be confined to a thorough explanation of the problem and the attempt made to effect as harmonious an adaptation as possible to the different standards of the majority, especially as homosexual practices are punishable under the existing penal code and its proposed modifications.

REJUVENATION

By Dr. F. Prange

More than twenty years ago Harms introduced a method of implanting young gonads of the same sex into an elderly subject; this operation was followed by a transitory diminution in the signs of age and a short recrudescence of sexual desire associated with a return of semen-production which could be demonstrated histologically. The method was later systematized and developed by Steinach, who called it "rejuvenation" on account of his success in prolonging by implantation the physiological life of rats by about one-third. He then performed extensive experiments on man, chiefly consisting in the ligation of the vas deferens on one or both sides, or of the efferent ducts between the testis and the globus pallidus of the epididymis, in order that the consequent blocking of the seminal secretion might exert a stimulating effect upon the testicular parenchyma. In women the implantation of ovaries remained the surgical method of election. The irradiation of the gonads of either sex by X-rays or diathermy has also recently been employed. The results of this "rejuvenation", which has now been given the more modest title of "physiological war on old

age " (physiologische Altersbekämpfung), have varied considerably in the reports of different authorities. The blame for this should not be laid solely upon the method, for the indications, especially in the earlier years, were made much too broad, and it was even applied to patients suffering from the cachexias of carcinoma. In premature senility, however, it has achieved some success. In some of our cases the growth of hair has become more vigorous and a general increase of power and sexual desire has taken place, together with a fall in the blood-pressure (Schmidt). In women ovarian implantation is most likely to be successful in the pyknic type, but the prospect is far less favourable in the spare and sexually inverted types (Löser). In certain cases, and when the ordinary physio-therapy, diet and drugs, fail, this method of " rejuvenation " may be tried, albeit, in my opinion, without any undue optimism. As a surgical operation it carries no especial risk.

DISEASES OF THE PINEAL GLAND.

Anatomy and Physiology.—" In adult man the epiphysis cerebri or pineal gland consists of a flattened protuberance about 1 cm. by 0·5 cm., connected by the dorsal lip to the habenular commissure and by the ventral lip to the posterior commissure. The pineal recess runs downwards between the two lips from the third ventricle " (Falta). The pineal gland maintains or increases its volume until growth is complete. It is chiefly composed of nerve elements—glial and neural cells—and of the specific epithelial " pineal " cells, which lie between the network formed by the processes of the glial and neural cells. These pineal cells, with their large nuclei and abundance of chromatin, also contain globular bodies known as corpora amylacea (brain sand). Recent investigation has shown that although regressive changes in the pineal gland may begin in youth, functionally active tissue may still be present in it in old age, despite a considerable amount of degeneration and cyst-formation.

It must also be remembered that the question of the endocrine properties of the pineal gland is still under discussion, and that some authorities doubt that it is an endocrine gland at all. Nevertheless, it must be concluded on clinical grounds that the pineal is extremely significant for the genital and other development before puberty, especially, as Marburg holds, since failure of the pineal function conditions premature development. Other authorities hold hyperpinealism, resulting from tumour, to be the cause of precocious puberty. The results of experiments and of feeding-tests have not been uniform.

Premature Sexual Development (Hypergenitalism)

This rare disease picture is not adequately described by the usual term of pubertas præcox, because in addition to

the early appearance of puberty the whole physiological and often the psychical development is premature as well.

Pathogenesis and Symptomatology.—The pathogenesis varies. Attention should be paid to three endocrine factors: tumour of the pineal gland (Marburg), tumours of the adrenal cortex, and tumours of the gonads in either sex. Infantile hypergenitalism is extremely rare in the absence of a growth in one of these glands.

Tumours of the pineal with premature puberty have hitherto been observed practically exclusively in boys, while growths in the adrenals and gonads may cause this disease in either sex.

Tumours of the pineal gland (sarcomata, carcinomata, cysts, teratomata, gummata, etc.), which appear before the age of twelve at the latest, lead in boys to a striking development of the primary and secondary sexual characteristics. The penis, testes and prostate of a boy of three have the same appearance and function as in a normal child of fourteen to sixteen. Erection is experienced, and tendencies to masturbation are observed. At the same time there is a growth of pubic and axillary hair, and often of facial hair as well. The height and girth increase rapidly, and the epiphyseal junctions and bone development are those of a child of five to ten. The dimensions of the body correspond to the genital development and not to the patient's age. The voice—on account of the abnormal growth of the larynx—becomes deeper and more mature. The hands and feet and the skin generally become coarser and more powerful and lose their soft and childish appearance.

The psychological development is abnormally early in some cases, but in others it corresponds with the patient's age. Abnormal obesity is also sometimes observed.

In addition to these trophic symptoms most patients exhibit local and general cerebral symptoms, which may, however, be very much in the background in small children with hypergenitalism. The general symptoms are those of increased cerebral pressure: headache and compression, malaise, vomiting, slowness of the pulse, and sometimes

choked discs. Local symptoms of pineal tumour may take the form of nystagmus, paralysis of the optic muscles, and of conjugate deviation, ataxia, convulsions, etc., as in lesions of the region of the corpora quadrigemina with pressure on the fourth ventricle. The end-result may be death in coma. It should be noted that, in the very rare cases in which it occurs in adults, pineal tumour is usually much more easily recognizable, but there usually seems to be no genital hypertrophy, either functional or morphological. On the contrary, functional impairment and atrophy have been observed. Both pineal obesity and cachexia may occur in adults.

The pathogenesis is obscure because of the great diversity of the results of investigation into the physiological significance of the pineal. Many authors cannot accept the opinion that the normal pineal gland inhibits sexual development, and it is also unlikely that excessive function of the gland, which has been suspected by many to exist, leads to hypergenitalism. A number of writers (F. H. Walter) dispute that the pineal has any endocrine properties at all. Nevertheless it must not be overlooked that both experimental extirpation and anatomically demonstrable hypoplasia of the gland have produced hypergenitalism, and that on this account a hypopinealism is by far the most probable factor in the ætiology. As in the many and various pituitary syndromes, so also in pineal hypergenitalism, the theory has been put forward (supported by a case of Schmalz's) that the condition is a purely cerebral one, caused by some lesion of a putative centre situated in the hypothalamic mid-brain and controlling the genital growth and function.

Premature genital development associated with *tumours of the adrenals and gonads* takes much the same course as that conditioned by the pineal, except that here female patients are in a large majority. In cases of adrenal tumour the development of the external and internal genitalia, the appearance of menstruation and subjective sexual sensations, the growth of the skeleton, and with it the height of the patient and the advent of the secondary sexual characteristics, all occur very early. The opinion expressed by some writers, that the bodily dimensions correspond in the

suprarenal form more to the patient's age than to her genital development, is doubted by H. Zondek.

The **diagnosis** of cortical tumours, especially adenomata, of this kind, if they are not palpable, is naturally extremely difficult. An X-ray picture will sometimes facilitate it if the growths are very large. The functional and other clinical criteria of this form of suprarenal hypertrophy are extremely uncertain.

Tumours of the gonads are much easier to diagnose, on account of their palpability, especially teratomata, carcinomata or sarcomata of the testis or the ovaries in small children.

Hypergenitalism is less commonly associated with gonadal growths than it is with tumours of the pineal and adrenals, but the syndrome in either sex and the general premature development are practically the same.

In diagnosing incipient hypergenitalism it is necessary to distinguish it from gigantism. The final difference is obvious, for cases of hypergenitalism, if they survive, do not grow abnormally tall but rather tend to be short. Their epiphyses unite as early as the eighth or tenth year. Moreover, hypergenitalism is not a feature of most gigantism, especially the pituitary forms, in which the genital function is generally subnormal.

The **prognosis** corresponds to the underlying cause, *i.e.* to the nature of the tumour and its amenability to treatment. A few patients, who have no malignant growth, live to the ordinary span of life. Others, whose development has been premature, age abnormally early. Cases have been described of youthful "old men" who died of "senile exhaustion" at ten or twenty.

The treatment of tumours of the adrenals and genitals is naturally surgical. Their successful extirpation has been followed by involution and a return to normal development. In theory pineal tumours can also be treated surgically or by X-rays, but as far as I am aware no certain knowledge exists about the results of such treatment. Pineal extract is said to have brought about improvement in many cases.

Other Genital Dystrophies of Suprarenal Origin

Hyperplasia or tumour formation in the adrenal cortex during fœtal life may give rise to spurious hermaphroditism or pseudo-hermaphroditism of the feminine variety. Tumours of the adrenals appearing in adult women may lead to the development of *virilism* or hirsutism (Apert). The breasts and internal genitalia atrophy, and premature menopause and frigidity set in. Hair grows more or less vigorously on the face, and the body hair, especially that of the genitalia, thickens and takes a virile form. The shape of the body and face becomes manly, and the voice may deepen. Sometimes the psychical outlook tends to become masculine, and occasionally hyperpigmentation and adiposity are observed (H. Strauss). Apart from these changes, the symptoms of adrenal tumour are usually present, with or without nephritis and raised blood-pressure. It is a striking fact that the syndrome is almost entirely confined to women. Out of about forty cases only two were men (both of whom had an abnormal mammary development and one of whom had secreting mammary glands). Although I have seen numerous cases of hypernephroma in men, in none of them has there been any change in the genitalia and secondary sexual characteristics (at any rate in the direction of feminism). *Hirsutism* seems important, as it sometimes gives early warning of the development of a hypernephroma, which experience shows is liable to go undiagnosed for a long time.

The pathogenesis of this " genito-suprarenal " syndrome is generally referred to excessive function caused by tumours of the adrenal cortex, which are usually adenomatous. This explanation is also applied to genital dystrophies in adults.

The only **treatment** is an attempt to remove the tumour surgically, or if this is impossible, by X-rays.

Premature Senile Involution

Now that the various forms of premature maturity and development have been described, it will be appropriate to consider the relatively rare condition of morbid pre-

mature senility, which is classifiable with fair certainty as an endocrine or central trophic disorder. It is not always pathological; in fact, in mild forms it is a slightly abnormal but at the same time a physiological occurrence. Every reader knows of individual cases and families in which the men at forty become pot-bellied or withered, grey and bald, and the women matronly. Premature greying of the hair may be regarded by itself as a fairly reliable superficial sign of premature senility; as everyone knows, it tends to run in families. The same is true of baldness in men and early menopause in women, and to a certain extent also of the familial age-disease of arteriosclerosis.

It is also recognized that certain endocrine disorders lead to early senescence. One of the most common of these is Graves' disease, which brings about premature withering and greyness in a most striking manner; I know women of forty who would be taken for over sixty. Myxœdema, on the other hand, provided it is properly compensated with thyroid extract, preserves its victims remarkably well. It is true that untreated myxœdema patients look wretchedly ill and that their deposits of water and fat make them look older than they are, but, as far as my experience goes, hypothyroidism does not produce any marked degree of senescence. The conclusion at which Vermehren and Lorand arrived a long time ago, identifying old age with chronic myxœdema, is thoroughly one-sided and erroneous. The peculiar fact that the hair of myxœdematous patients usually retains its pigment until well into the seventies and does not turn grey, refutes the hypothyroidal theory of senescence. Other endocrine disorders besides Graves' disease, however, lead to premature old age. It has been observed in diseases of the adrenal cortex, though it certainly does not result from true Addison's disease. The severest form of early senescence is seen in Simmonds' pituitary cachexia, in which there is a complete failure of the function of the anterior lobe of the pituitary.

There are also cases of premature senility which do not come into any of the classes of endocrine disorder that have been mentioned. The patients, who are more usually

women, begin to age noticeably at the beginning of the thirtieth year ; their hair thins and turns white and their skin becomes dry, withered and wrinkled. They develop mild senile kyphosis and acquire a senile facial expression and cast of mind. On examination they show involution of the internal and external genitalia and mammæ, and a thinning of the body hair. Every doctor knows these women of forty who look sixty and sixty-five. H. Zondek, who has carried out some exhaustive researches on these cases, has found clinically, in addition to the senility, low blood-pressure, " drop-heart ", senile involution of the genitalia, and a normal blood-sugar. The post-mortem examination of one patient of 36 revealed a general atrophy of the internal organs (liver, spleen and kidneys), and especially of the glands of internal secretion, just as in old age. The atrophy and proliferation of connective tissues were most marked in the adrenal cortex, anterior lobe of the pituitary, and especially in the ovary, but much less in the thyroid.

We can therefore support H. Zondek's conclusion that the cause of this very early senility is a very slow and sometimes quite benign form of pluriglandular insufficiency, in which the adrenal cortex, anterior lobe of the pituitary, and above all, the ovary, play the principal rôles. In the cases of Graves' disease with early senility which have been referred to, secondary pluriglandular lesions had an even greater ætiological significance than the hypertrophy and disorder of the thyroid gland. It is of course quite possible that, as in other diseases apparently endocrine in origin, premature senile involution may be caused by a pure lesion in the mid-brain centres instead of by an endocrine disorder.

Infantilism

By infantilism is understood a general inhibition of the development of the organism which keeps the patient either temporarily or permanently at a stage of growth earlier than that appropriate to his age. Infantilism is the product of various factors, and for practical purposes can be divided into two main groups : (1) the genuine form, con-

ditioned by a pluriglandular disorder or a corresponding disorder of the trophic centres; and (2) the secondary form caused by outside influences, such as infection, intoxication, diseases contracted in childhood, hunger, vitamin-deficiency, etc.

Many writers, for example L. Borchardt, distinguish other groups: one due to lesions of the germ plasm (blastophthoria) or of the fœtus (embryophthoria), two syndromes which can be induced experimentally but which as yet do not possess much clinical significance. It is unnecessary, however, to adopt a concept of monoglandular infantilism conditioned by the thyroid or pituitary or by a defective thymus; these conditions come under the headings of diseases of the respective endocrine organs, and for practical therapeutic reasons should not be separated from them.

Symptomatology.—As its name implies, infantilism first manifests its effects openly when the stage of bodily and mental childhood is due to come to an end, *i.e.* at puberty. Naturally, however, the physician may suspect its existence even in early childhood; the developmental defects which condition it must obviously be present early in infancy. Nevertheless it is necessary to exercise great care in diagnosing infantilism in small, delicate children, such as seven-months babies and twins. Time and again children of this type shoot up vigorously, either before or after puberty, and quickly attain a normal development.

While infantilism always shows itself in childhood by the *retardation of skeletal development* and consequently of the stature and girth, at puberty the symptoms become much more obvious. The most striking of them is the child's shortness and slenderness. At sixteen they look like twelve, and young ladies of nineteen are taken for schoolgirls. In many patients the proportions are completely childish, with the child's fat-deposit, chubby face and other characteristics; in others the impression of infantility which should be conveyed both by the appearance and the proportions is disguised by a pronounced asthenic habitus, a wasting disease, or under-nourishment.

Some cases of infantilism, especially female ones, look

like ordinary grown-up people in miniature. Genuine dwarfism, of course, has nothing to do with infantilism.

Arrest of genital development is one of the most important signs, and doubtless also an ætiological factor. The external and internal genitalia in both sexes remain infantile and underdeveloped—but not aplastic—for a long time. Sexual desire, erection and masturbation are completely absent in the boy of seventeen, and the girl of eighteen has no periods and is quite frigid. The secondary sexual characteristics are also absent. Growth in the boy of facial and bodily hair and breaking of the voice, and in the girl of axillary and pubic hair and maturing of the figure, also fail to appear. The hair and skin remain infantile ; the latter keeps its softness and is free from the typical blemishes of puberty, such as comedones and acne. The heart and vessels are small and narrow, and the blood-pressure is low, as in childhood.

Fig. 44. — Infantilism in two boys of 13 and 15 respectively. The first has the appearance and size of a child of 7 or 8 and the other of one between 11 and 12. (Author's cases.)

There is nothing especially abnormal to be found in the *metabolism*, though infantile characteristics (such as a relatively high gas-interchange) may persist here as elsewhere. In most cases, however, we have noted no gross disturbances of basal metabolic rate and specific dynamic protein action. Except for lymphocytosis, which is common, the blood shows nothing characteristic ; true anæmia is not one of the symptoms of infantilism.

The *nervous system* is nearly always free from organic lesions. The mind, on the other hand, is an accurate reflection of the body ; an infantile affective disposition and a childish intellect are very often found, or at least indicated. Even children with a high degree of intelligence surprise one by their extreme emotional sensibility. The great mental acumen, wit and depth sometimes seen in many forms of true nanism are nearly always entirely absent in cases of infantilism.

The *endocrine organs* in both " genuine " and " secondary " cases of infantilism show no changes, palpable or otherwise, and the gross and obvious symptoms of pluriglandular insufficiency (*q.v.*) are certainly not part of the picture. Moreover, as has been said already, for the sake of diagnostic clarity and for the purposes of treatment, we prefer to exclude infantilism due to deficiency of the thyroid and pituitary.

Ætiology.—The causes of infantilism are, as we have already said, very various. For the large group of " genuine " infantilism, which is very rarely familial or hereditary, we must assume some impairment of the germ plasm and an inhibition of growth conditioned by a pluriglandular or central disorder.

In normal times the following must be considered as the chief causes of the secondary form :

(i) Early or congenital infectious diseases (syphilis, tuberculosis, malaria, leprosy, etc.). Infantilism is very common with tuberculosis, especially the chronic peritoneal form.

(ii) Early metabolic disorders, above all, diabetes, and intoxications (for example, by alcohol, nicotine and lead). Alcohol is so well known a cause that there is a popular saying, " Children who drink schnapps never grow any more ".

(iii) Congenital heart defects. These are very often associated with infantilism. The connection is not, in my opinion, an occult ætiological one, but merely the quite comprehensible association of two kinds of dysplasia. Congenital heart defects

do not seem to lead inevitably to infantilism. I have seen in fully developed adults the congenital heart troubles (for example, pulmonary stenosis) which in others are associated with infantilism. This is also true of other hereditary diseases. Infantilism is relatively common in hæmolytic icterus, but rarer in the well-known forms of hereditary degeneration of the nervous system.

(iv) Underfeeding has indubitably been the cause of many cases of moderate infantilism. Everyone who inspected recruits of seventeen or eighteen in the year 1918 saw large numbers of youths whose genital and other development was that of boys of fourteen ; they presented typical pictures of growth-arrest through privation.

(v) The cause of infantilism may lie not only in an insufficient diet but also in defective assimilation ; an example is the intestinal infantilism of Herter and Heubner. In patients who have suffered for long periods in childhood with disorders of the stomach this form has been referred to defective absorption of nourishment, and also—on rather inadequate grounds—to a shortage of lipoids, like the infantilism of starvation. Whether this infantilism of Herter and Heubner can lead to an inhibition of growth persisting until the late twenties is uncertain, and at any rate impossible to prove.

The **diagnosis** must first of all eliminate gross monoglandular and pluriglandular syndromes, especially infantile athyroidism, hypothyroidism and cretinism ; diseases of the pituitary, especially pituitary nanism ; and all typical forms of dwarfism. The well-marked forms of pluriglandular insufficiency do not come within the nosological territory of infantilism, except that between infantilism and their milder varieties transitional stages may be seen. Similar transitions may occur between true dwarfism and infantilism. Patients have been known who came under the heading of dwarfism

in early childhood but who have had to be classed as cases of infantilism after puberty.

Course and **prognosis** depend on the cause. If it lies in an incurable or very advanced disease, such as congenital heart defect, tuberculosis and severe intractable diabetes, no improvement is likely to take place in the infantilism. In all cases in which the underlying cause may be removed (underfeeding, neglect, syphilis, hæmolytic icterus and controllable diabetes) the obstacle to growth may some day be removed and the development proceed normally. This of course applies especially to endocrine conditions which are capable of being compensated by organotherapy. In spite of these therapeutic possibilities, however, it must be admitted that many cases of infantilism pass their whole lives without overcoming the factor which inhibits their growth.

The **treatment** is that appropriate to the underlying cause, whether it be hunger, disturbances of nutrition, gastric catarrh, syphilis, alcoholism, diabetes or hæmolytic jaundice. The physician should always aim at a treatment directed to the cause. When disorders of the function of one or more endocrine glands seem to be present, hormone preparations such as thyroid or pituitary extract or direct treatment of the pituitary should be tried.

STATUS THYMO-LYMPHATICUS

Anatomy.—The thymus is a flattened organ situated behind the upper third of the sternum. It increases in size and circumference from birth until puberty, but thereafter undergoes gradual involution. Its weight, according to Hammar, has been found to be 13·26 g. at birth, 37·52 g. between 11 and 15, and 19·8 g. between 26 and 35. When the thymus is larger than this in an adult the condition is called " persistent thymus ". Recent investigations, carried out upon persons who have died suddenly from injury, showed a relatively high incidence of persistence of the thymus, and it is therefore reasonable to suspect that the greater (and apparently normal) involution of the gland may have been due to the wasting effects of illness. It is also certain that the size and condition of the gland depend very largely upon the diet (Lubarsch and others). Anatomically the thymus belongs to the lymphatic apparatus. Its medullary substance chiefly contains polymorphous reticular cells and Hassall's corpuscles, which contain a horny-like mass (microchemically this reacts like thyroidal colloid). The periphery of the gland contains lymphocytes.

The function of the thymus has not yet been fully elucidated. It has been proved clinically and experimentally to exert an influence over the skeletal growth. When young animals are deprived of their thymus the bones cease to grow and become abnormally soft and brittle, and the animals remain dwarfs. The conclusion is that the thymus influences in some way the mineral, and especially the calcium metabolism. Its effect upon the genital function and development and upon the blood formation, especially that of the lymphocytes, is not yet quite clear. It has apparently no specific significance in tetany or spasmophilia. According to Wiesel, one function of the thymic secretion is to stimulate the vagus.

Clinical Data.—Status thymicus is the morbid condition which Kopp in 1855 first alleged to be due to persistence of the thymus. It is chiefly known because of the attribution to it of sudden deaths of children and young people either in stridor and cyanosis or, more often, in narcosis, after an injection of diphtheritic serum, or a fright, or immersion in cold water. The old theory of a purely mechanical compression of the air passages by the gland has been almost universally abandoned, and such deaths are not held to result from sudden paralysis of the heart or circulation. H. Zondek frankly accepts the idea of " vagal death ", and Hering that of ventricular fibrillation.

Paltauf made an important discovery when he established that status thymicus was associated with hypoplasia of the heart, aorta and vessels, and a general swelling of the lymphatic apparatus. Another notable contribution was that of Wiesel and Hedinger, who found hypoplasia of the adrenal in pure status thymicus, while in status thymo-lymphaticus the chromaffin apparatus appeared to be intact. Nevertheless the conundrum of sudden death from status thymo-lymphaticus has not yet been solved, and the diagnosis often looks very like a way of escape from difficulty or a loophole for exculpation.

Hyperplasia of the thymus in life is very difficult to confirm and can never be reliably established with certainty by percussion. Its detection by X-rays appears very uncertain to critical radiologists. Indirect symptoms, for example a tendency to stridor, are also untrustworthy. That typical bronchial asthma has nothing to do with hyperplasia or dysfunction of the thymus seems to me proven, and I do not agree with the distinction of a form of asthma by the name " asthma thymicum ". (The fact that alleged " asthma thymicum " is relieved by X-ray treatment of the thymus proves nothing, for it is relieved equally well by irradiation of the spleen.)

Sarcomata and carcinomata originate in thymic rests, and contribute nothing to the morbid pathology of the gland. One case of primary cancer of the thymus investigated by myself developed pluriglandular metastases, especially in the

pituitary, followed by diabetes insipidus, acromegaly, impotence and bronchial asthma.

Persistence of the thymus has been found in many cases of pseudo-paralytic myasthenia: the cell-groups found in the muscles have been explained, to my mind incorrectly, as metastases of the thymus. X-ray treatment of the thymus area gave uncertain results in my cases, and in one of them thymectomy was followed by death. Taking one thing with another, I think that the thymus explanation of myasthenia is neither proved nor probable.

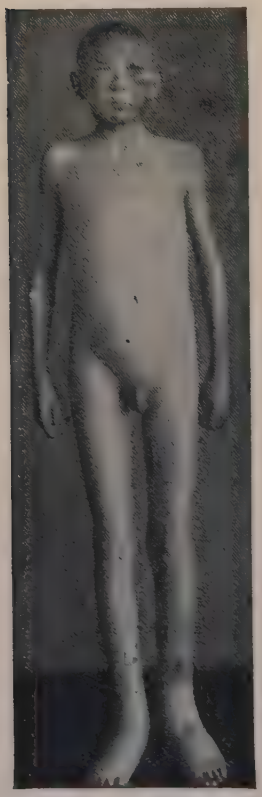


Fig. 45.—A boy of 16 with status thymo-lymphaticus (eczema, œdema of the legs, hypoplasia of the genitalia). (From H. Zondek.)

For an account of the part played by the thymus in Graves' disease the reader is referred to the appropriate chapter. This is the commonest thymic syndrome that can be identified. It has already been remarked that the vagotonic "symptoms" of Graves' disease (hyperidrosis, occasionally bradycardia, eosinophilia, etc.) have been classed as results of an excess of thymus secretion, but this proposition is very difficult to prove. H. Zondek regards the hyperplasia of the thymus in Graves' disease as an attempt by the organism to balance the increased stimulation of the sympathetic by a corresponding rise in the vagotonic activity of the thymus. Moreover, the therapeutic and physio-pathological results of surgical and radiological treatment of the thymus have not yet been satisfactorily assessed.

The **pathology** and **clinical picture** of status lymphaticus seem to be better established, but it must be noticed that even here authorities differ very widely in the definitions and

classifications. By "lymphatic" children and young people we mean pallid, flabby, pasty youngsters with a tendency to eczema, colds, asthma and œdema, who suffer from transitory or permanent swelling of the glands, and frequently from enlargement of the pharyngeal and palatine tonsils. The glandular swelling chiefly affects the cervical, submaxillary, occipital, and inguinal glands, and the adenoid growths cause a liability to certain infections, such as sore throat, colds and conjunctivitis. The tendency to œdema, asthma, rhinitis and eczematous skin complications shows the syndrome to be interchangeable if not identical with that known to pædiatricians as the "exudative diathesis". Some writers claim to have found hyperplasia of the thymus in many cases of status lymphaticus.

In lymphatic children the blood-pressure is reduced and the blood-sugar abnormally low; both these phenomena are related to diminished function or development of the chromaffin system. In addition to this there is usually secondary anæmia with relative or absolute lymphocytosis. In one of our cases the gas interchange was not impaired. The water economy undergoes change, and the Volhard water-test showed delayed excretion with a normal range of concentration. Many patients have hypoplasia of the genital organs, mostly, as in infantilism, of the type which causes delay in maturity, and a corresponding deficiency in the development of the secondary sexual characteristics.

The children are usually fatter than normal, although quite a number are thin and sickly. They have hardly ever attained to their proper height. The important ætiological factors are the inherited endocrine disposition on the one side, and on the other, external factors such as faulty diet, infections and intoxications during the first years of life. This ætiology is another very close point of contact with infantilism (*q.v.*), with which many cases undoubtedly show an identical picture.

The **treatment** of status lymphaticus in young children should be especially directed towards the diet. As in the "exudative diathesis", milk, all kinds of fat and eggs should be reduced as much as possible, and a diet of lean meat, fruit,

vegetables, potatoes and cereals should be substituted. Among calcium preparations, calcium chloride (not less than 3 grm. per diem) is often effective against exudative disorders. Bracing treatment, natural and artificial sunlight, and brine and sea baths often have an excellent effect. In addition to these, all other exogenous causal and predisposing factors, such as infections and disorders of metabolism, should be taken into account, just as in infantilism.

If hyperplasia of the thymus is suspected on conclusive grounds X-ray treatment is indicated, and should also be tried before the hazardous operation of thymectomy is undertaken. The efficacy of irradiation has been demonstrated theoretically in man as well as in experimental animals.

The **differential diagnosis** must first of all eliminate tuberculosis of the glands, lungs and intestines ; it is capable of imitating and sometimes of causing the whole lymphatic and exudative syndrome. Care must be taken to eliminate leukæmic and non-leukæmic lymphadenomata, lymphogranulomatoses, lymphosarcomata, infantile forms of anæmia, and childish hypothyroidism. A watch should also be kept for infantilism, as it is fairly often associated with status lymphaticus.

PLURIGLANDULAR INSUFFICIENCY

The syndrome of pluriglandular insufficiency is difficult to define nosologically on account of its protean manifestations. For the sake of diagnostic clarity we prefer to keep the term " pluriglandular insufficiency " whenever possible for the type originally described by Claude and Gougerot as " pernicious thyro-testiculo-pituitary-subadrenal insufficiency ". We propose therefore to apply it only to patients who have previously exhibited definite, chronic, relatively mild, pluriglandular symptoms, without, on the one hand, any well-marked underlying disease (such as osteomalacia, Erb's or myotonic dystrophy, or sclerodermia), or, on the other hand, without suffering or having suffered from any disease in which a lesion of one gland is markedly predominant. The latter groups include the " school-girl " type of genito-sclerodermatic degeneration, described by Von Noorden and others, and other obscure chronic forms of cachexia.

The clinical concept of pluriglandular insufficiency as defined by Claude and Gougerot would appear to coincide more or less with W. Falta's term " multiple glandular sclerosis ". Nevertheless I should like to point out that I myself, on clinical and anatomical grounds, do not use Falta's concept. The anatomical sclerosis recognized by Falta is absent in many cases who correspond absolutely to the Claude and Gougerot type. It is of more practical value to content ourselves once and for all with the clinical concept and name of " pluriglandular insufficiency ".

The **symptomatology** of this type may be recognized from the following description of a case :

A man of about forty, quite healthy before admission, moderate drinker, no infections, married and without children,

complained—after a short influenzal attack—of a gradually increasing swelling of the abdomen, legs and whole body, together with frequent attacks of diarrhœa. There was also a slow pigmentation of the sites of predilection, and abnormal tanning of the face and hands after short exposure to the sun ; the nails and teeth were fragile. There was a severe loss of hair from the head and body, and complete disappearance of sexual desire and potency, with atrophy of the penis. He also suffered from great debility, and had a subnormal temperature.

Examination showed a man of delicate build, very pale but with dark brown pigmentation of the face, hands, genitalia, etc., and firm œdema of the legs, abdomen and back, less pronounced on the upper half of the body. No trace of cardiac insufficiency was discoverable ; the urine was chemically and microscopically normal. The blood-pressure was only 110-60. The lungs were normal ; there was slight ascites but no abnormality of the liver or spleen. The face had become quite hairless, and the voice had grown high and boyish or feminine. The scalp-hair came out very easily, and was dun-brown and not grey. All the body-hair, especially that of the genitalia, had disappeared. The penis was small, and the testes and prostate very small and hard. The thyroid was not enlarged. There were no symptoms of Graves' disease, tetany, or organic nervous disorder. The mental condition at the outset was slow, dull and stupid, and at the end confusional and delirious.

There was achylia and the stools were very fatty. The pupils showed a high degree of adrenalin mydriasis ; no glycosuria followed the injection of 0·7 mg. of adrenalin subcutaneously. There was a slight degree of secondary anæmia, with 35 per cent lymphocytosis.

The cachexia, œdema, hair-falling, pigmentation and mental disorder all increased, and the patient died about a year after admission.

The only organs which it was possible to examine post mortem were the pancreas and adrenals, which exhibited no histological changes. Nevertheless, in the light of the symptoms we must assume an insufficiency of these organs, and also of the thyroid and gonads.

Course and Symptomatology.—If disorder of one or other of the glands appears more prominently, the syndrome will

be modified. Instead of the œdema, for example, a fair and even an extreme degree of adiposity may be present at the outset. This is not apparently encountered so much in the rapid pernicious class of case as in the slowly developing mild ones (H. Zondek). Again, the signs of defective adrenalin secretion may manifest themselves in more or less marked symptoms of Addison's disease (hypotension, adynamia, general pigmentation). Severe bony changes may occur, even in adults. The most conspicuous complaint —particularly in young patients—may be tetany with its concomitants of muscular hyper-sensitivity and cataract. This is generally absent in the type of patient we have described. If the pancreas is much involved, transitory or permanent symptoms of diabetes may appear. The preponderating symptoms, on the other hand, may be cutaneous, and especially of a sclerodermic character. Finally, there are cases in which insidious cachexia and marked premature senility predominate (cf. the section on premature involution).

The *onset* of the pernicious form of Claude and Gougerot usually occurs in youth and middle life, but Krabbe and I have also seen it appear in early childhood, and even congenitally. I think we must assume in these early cases that there is some congenital hypo- or dysplasia of the endocrine glands, which is most clearly demonstrable in the gonads and thyroid. From this basis the atrophic and sclerotic processes later on spread and develop. The involvement of the thyroid, gonads and pituitary in early cases and those beginning in childhood leads to a more or less severe inhibition of the skeletal growth, to dwarfism, defective mental development, obesity and the like. It must, however, be noted that pronounced defects of development, especially of the genitalia, may manifest themselves fairly often in the class of case that has been described, the pernicious type occurring in middle age.

While some cases of the Claude and Gougerot type progress relatively quickly and end fatally after a year or two, others, especially those which begin in early life, develop much more slowly and may last for one or even three decades. This is also true of the peculiar form described by Von Noorden under the name of "genito-sclerodermatic degeneration",

occurring in girls. The syndrome consists of cachexia (which may be pituitary), hypogenitalism, and symptoms of sclerodermia, occurring in previously healthy young women. I have already remarked that this type may also occur without sclerodermia but with the signs of acromegaly and xanthosis (the intense yellow pigmentation which is practically peculiar to diabetes).

Another juvenile form which I have described is the *hypothyroid hypogenital type* with congenital hæmolytic icterus complicated by diabetes. Insufficiency of the thyroid and gonads (L. Borchardt), another syndrome which occurs especially just after puberty, may be classified equally appropriately as a benign chronic hypothyrosis. Other cases with similar endocrine symptoms occurring at or after the menopause I prefer to class as more or less complete myxœdema ; I saw a good many of these in the years of scarcity. They usually run a mild course and yield to thyroid extract. When this syndrome occurs in adolescence and is accompanied by marked hypogenitalism, the picture corresponds exactly to that of Falta's " late eunuchoidism ".

The *disorders of metabolism*—respiratory, fat, nitrogen and glycogen—and of the water economy are due for the most part to and correspond with the disturbances in the function of the thyroid and pituitary. It is not possible to discover any uniformity in the blood-picture, but lymphocytosis is common ; polycythæmia is found more frequently than anæmia.

Anatomically, when changes can be demonstrated at all, the condition is probably one of primary atrophy (sometimes to only a quarter of the normal size), with a more or less advanced secondary sclerosis of the connective tissue in some or all of the endocrine organs, especially in the thyroid, gonads and pituitary. Sometimes, in addition, there is hyperplasia of other organs, such as the thymus. There are, however, cases in which both sclerosis and atrophy are lacking, even when the functional disturbances are so marked clinically as to suggest that they must have an anatomical foundation. This suggests the cerebral form of pluriglandular insufficiency referable, like Biedl's obesity, acromegaly

and other symptoms of apparently glandular origin, to a pure primary disturbance of the mid-brain area by tumour, encephalitis, trauma, and the like. The tumours are situated in the region of the pituitary, but do not ramify from it. L. Borchardt, Ratner, Ricaldoni and others describe cases of this kind in which the symptoms are similar to those of glandular origin. The diagnosis is usually impossible until autopsy. The prognosis is of course usually unfavourable, unless the disease process is a curable one, like syphilis.

The **ætiology** of typical pluriglandular insufficiency is in most cases obscure. There is a good deal of evidence for a primitive dysplastic or hypoplastic condition of the glands, a congenital "endocrine debility". We know from the work of Bartel and others that hypoplastic organs, especially lymph-glands and gonads, tend towards sclerosis of the connective tissue. In all the cases I have myself observed one or more dysplastic traits have been shown by the history to have existed in adolescence, and in some there have also been obvious signs of physical degeneration. In other patients, however, the glandular and general health seems to have been good right up to the time of onset. In many of these cases the cause can be shown to be syphilis, tuberculosis, or even alcoholism, which can, as we know from cirrhosis of the liver, cause proliferation of connective tissue. Quite astounding improvements in the symptoms have followed anti-syphilitic treatment. Other infections, such as influenza, typhoid and malaria, have naturally been incriminated. Others besides myself have seen pluriglandular insufficiency caused by pluriglandular metastases from a primary carcinoma of the remains of the thymus. It is quite probable that permanent starvation, as in true myxœdema, may also give rise to pluriglandular insufficiency, for the endocrine glands are especially susceptible to the effects of prolonged underfeeding.

The **diagnosis** is therefore often very difficult, for the definition of pluriglandular insufficiency has now been energetically fought over for a long time. It seems to be largely a matter of taste, for example, whether a sclerodermic dystrophia (Hans Curschmann) or a late osteomalacia, or a myotonic (or

sometimes an amyotonic) dystrophy or a myasthenia, accompanied by a large number of pluriglandular signs and symptoms, is to be called " true " pluriglandular insufficiency or merely sclerodermia, myotonic dystrophy, myasthenia or osteomalacia. Personally, however, I think it is a sounder plan in practice not to reckon syndromes of this kind as pluriglandular insufficiency in the narrower sense when the pluriglandular symptoms—which, though sometimes conspicuous, are often only slight—belong to a well-known disease entity with well-recognised clinical and anatomical characteristics, as they do in the instances I have cited. It works better in these cases to consider the pluriglandular phenomena as associated symptoms of the acquired or congenital dystrophy or dysplasia, and not as manifestations of the cause of the disease. In many cases of myotonic dystrophy my view has been confirmed (Hitzenberger) by the fact that the endocrine glands were unimpaired in spite of the clinical disturbances of function.

FIG. 46.—A woman of 40 with pluriglandular insufficiency. Insufficiency of the pancreas and adrenals and atrophy of the genital organs; emaciation. Note the surprisingly youthful expression. (Author's case.)

For the same reason I think it important in practice to distinguish from pluriglandular insufficiency well-known monoglandular syndromes, such as Graves' disease, Addison's disease, Simmonds' disease, myxœdema and eunuchoidism, in which one or more symptoms referable to the other endocrine glands are present, as it is quite natural that they should be. It should be noted, however, that Simmonds' pituitary cachexia sometimes imitates pluriglandular insufficiency very closely.

It is also necessary to eliminate carcinoma of obscure location, hypernephroma, Biermer's anæmia, lymphogranuloma and other cachexias, which are very difficult to distinguish at the outset from pluriglandular insufficiency.

The **treatment** in pernicious cases (see above) is usually a thankless and fruitless task, unless the origin happens to be syphilitic, when specific therapy is indicated. In relatively mild chronic cases the best treatment is naturally by glandular extracts in carefully adjusted doses. The results are often good, especially when the chief deficiency is in the thyroid and thyroid extract can be given. Similar preparations of pituitary substance, such as "Praephyson", a recent product, can be ordered for the pituitary symptoms. The gonadal symptoms may be relieved by preparations of the male or female genital gland. Insulin will exert an influence on the debilitated secretory function of the pancreas, and "Pancreon" will assist its excretory function. In treating pluriglandular insufficiency the physician must combine the various gland substances to suit each case, and not rely upon the ready-made commercial combinations. In most cases, however, this pluriglandular substitution treatment is useless.

APPENDIX

Dystrophia Pigmentosa

E. Leschke has just described by this name a combination of the symptoms of Recklinghausen's neuro-fibromatosis with those of endogenous pluriglandular insufficiency. Whether they constitute a clinical entity is still uncertain. It has been established for a long time that many cases—especially young ones—of Recklinghausen's disease associated with physical and mental dystrophia also show endocrine symptoms of many varieties, especially those of hypothyroidism. E. Leschke observed an arrest of growth with physical and mental infantilism and an increasing pigmentation (freckles, nævi and light brown spots) which usually appeared as early as the first year, often in combination with endocrine symptoms such as obesity, genital atrophy, defective function of the adrenals (hypotonia, hypoglycæmia, debility, etc.), vegetative disorders and changes in the carbohydrate, chlorine and water metabolism. Many cases also showed optic atrophy, and some had eunuchoid and pituitary gigantism. In others (Hans Curschmann, Galart), diagnosed as presenting Leschke's syndrome, hypothyroidism and sometimes osteomalacia predominated. The syndrome seems, like so many which start in early infancy, to be the expression of a relatively benign form of a pluriglandular dystrophy which has its roots in the constitutional disposition. Leschke denies the presence of gross disorder of the pituitary. If the thyroid insufficiency cannot be improved with thyroid extract, the prognosis and treatment do not appear to be hopeful.

Pluriglandular Syndromes in Nervous Diseases, Sclerodermia, and Disorders of the Blood

As an addition to the section on pluriglandular insufficiency I propose to describe yet another common pluriglandular syndrome, which sometimes occurs regularly in such a

stereotyped form in a certain class of nerve and other disorders that many authors have regarded it as causal. I have indicated elsewhere that the nervous diseases in which it is chiefly found are the myoneuropathies, especially myotonic dystrophy, myasthenia pseudoparalytica; a few cases of progressive muscular dystrophy (Erb), other inherited degenerative diseases, and, finally, certain symptomatic pictures referable to the corpus striatum and globus pallidus.

Myotonic dystrophy (atrophic myotonia) must be strictly distinguished from Thomsen's "myotonia congenita", in which endocrine symptoms are practically never present. In addition to the muscular wasting of the face, neck, forearms and lower legs, and to the myotonic symptoms, which are generally slight, there are certain quite stereotyped trophic changes, mostly referable to disturbances of endocrine function. These include cataract (beginning as posterior cortical cataract with opacity of the posterior pole and radiating extensions); frontal baldness; and disorders of potency and menstruation, frequently accompanied by atrophy of the testes and sterility, but hardly ever by changes in the secondary sexual characteristics, and never by gigantism or obesity. Chvostek's facial sign is often seen, but rarely genuine tetany. A constant finding is a general wasting and emaciation, and great difficulty in getting the patient to "fill out". Dyspeptic disorders, with or without impairment of the secretory or motor functions of the alimentary organs, are the rule. H. Zondek and Maas found a marked lowering of the nitrogen metabolism, but normal metabolism of calcium and phosphorus. In a few cases I found a very large falling-off in the respiratory basal metabolic rate. The blood shows little abnormal, but there is often a lymphocytosis and eosinophilia with a normal blood chemistry. Sweating, lachrymation, acrocyanosis, over-sensitivity to cold, hypothermia, and other vegetative symptoms are common; the pharmacological tests on my patients for vago- and sympathicotonia were uncharacteristic but never showed a rise. Goitre — practically always without thyro-toxic signs — kyphosis and lordosis are not uncommon, but general osseous

atrophy is more rare. In most cases I found various grades of psychical disturbance of a degenerative kind.

Ætiology.—It is reasonable to assume that all these symptoms, some of which certainly depend upon endocrine factors while others seem practically unconnected with the endocrine system, are conditioned by pluriglandular disorders. It is, however, very doubtful whether the glandular condition has any causal significance for the disease. There is plenty of good evidence that it has not, as, for example, the completely negative endocrine findings in a case of Hitzenberger's that came to autopsy. I think it possible that the cause of the whole myo-dystrophic syndrome lies in congenital dysplastic defects in the vegetative centres of the mid-brain ; the vegetative innervation of the plain musculature has recently been shown to bear closely on its trophic and other functions.

In *myasthenia pseudo-paralytica* the intermittent fatigue-paralysis of the muscles of the head, trunk and limbs (with Jolly's typical myasthenic electric reaction) is also associated quite frequently with gross endocrine disturbances. I have seen hypoplasia and aplasia of the genitals accompanied in women by virilism, and I have also seen in myasthenia a large number of goitres and incomplete cases of Graves' disease, an observation which other authors have confirmed. In some cases I found Chvostek's and Erb's facial sign. Moreover, in 55 per cent there is persistence of the thymus. In view of these data it is possible to understand why some writers have argued that even myasthenia has an endocrine ætiology, that it is, for example, a manifestation of chronic hyperparathyroidism. However, the occurrence of stigmata of tetany due to parathyroid insufficiency proves that this view is wrong, and, as we have said, it is as yet impossible to diagnose hyperparathyroidism. Moreover, the theories which refer myasthenia to excessive secretion of the thymus or of the thyroid have equally little to support them.

The inconstancy of the endocrine symptoms makes me prefer not to look on them as expressions of the cause of the disease, but rather as associated symptoms of a malady whose nature and cause are still obscure and of

which the muscular symptoms are another manifestation. That the inherited constitution plays a significant part also in the development of myasthenia late in life is shown by the relative frequency of gross dysplasias and aplasias and the fact that the disease is sometimes hereditary.

The same is true of *Erb's progressive muscular dystrophy*, except that endocrine symptoms are here extremely rare. I have only once seen it in association with thyro-hypoplasia, and Rohr says the same thing. Very occasionally it is combined with dystrophia adiposo-genitalis, with obscure pluriglandular symptoms, or with genital hypoplasia and infantilism together. In most cases there are no endocrine stigmata at all. My colleague Fr. Bachmann, who has carried out investigations on advanced cases, found no metabolic or other changes of any kind to suggest endocrine disorder. Peritz' view, that it is due to hereditary disorder of the parathyroid, should be rejected as without foundation. The scanty and quite inconstant endocrine phenomena are an associated part of the symptom-complex of Erb's muscular dystrophy, and are not in any way an expression of the cause.

It is possible that the primary site of myasthenia and Erb's dystrophy alike may lie in the vegetative and metabolic centres of the mesencephalon.

Isolated endocrine symptoms also occur in diseases of the globus pallidus and corpora striata as well as in the so-called myoneuropathies. Various anatomical changes in the parathyroid have often been found in *paralysis agitans*, but as far as I know, tetany, the stigma of disordered parathyroid function, has never been seen. Symptoms of myxœdema and Graves' disease have been reported occasionally. This is another condition in which the theory of hypoparathyroidism has made a fleeting and ghostly appearance.

Authentic endocrine symptoms have also been observed — very rarely — in Parkinsonism following encephalitis lethargica.

In some cases of *Wilson and Strümpell's disease* atypical signs of endocrine hypoplasia, especially hypogenitalism and infantilism, have been observed, in addition to the extra-pyramidal spasm, tremor, convulsions and dementia.

I once saw cataracta cærulea. The liver and spleen are, however, constantly involved, showing hypertrophic cirrhosis. The suggestion that the hepato-splenic change is primary and the disease of the corpus striatum secondary is not, however, a very likely one. Here again it is necessary to regard the cerebral and intestinal disease-process as an associated part of a larger process of obscure ætiology.

Some cases of *familial myoclonic epilepsy* (Lundborg) present hypogenital, infantile, hypothyroidal or hyperthyroidal features and, though very rarely, pituitary symptoms such as acromegaly. These again can only be taken, in agreement with A. Westphal, as associated signs, pointing, like the epilepsy itself, to an inherited degenerative condition.

We have seen, therefore, that the diseases most commonly associated with endocrine symptoms are the myopathies (myasthenia, myotonic dystrophy and Erb's dystrophy) and the disorders of the globus pallidus and corpora striata.[1] Both these disease-groups have recently been classified as products of disordered function of the " sarcoplasma ", or of the sympathetic-para-sympathetic innervation of the muscles. As has already been said, the endocrine and the vegetative nervous systems share common centres in the midbrain, and this is the most probable source of these diseases and their common muscular and endocrine symptoms.

The most common of the ailments formerly known as " trophic neuroses " is *sclerodermia*, which is nearly always associated with endocrine symptoms. In company with other authors I have repeatedly seen, in diffuse and symmetrical sclerodermia, the signs of adrenalin deficiency (deep pigmentation, debility and hypotension); thyrotoxic symptoms such as exophthalmos, tremor and tachycardia; sometimes the symptoms of myxœdema, and fairly often those of hypogenitalism (impotence, amenorrhœa, frigidity and attenuation of the secondary sexual characteristics),

[1] Endocrine symptoms are occasionally found in other nervous syndromes of endogenous and exogenous origin, such as Friedreich's ataxia, syringomyelia, tabes, multiple sclerosis, progressive paralysis and true epilepsy. It is likewise impossible to do more than mention the endocrine symptoms which occur in many psychoses, especially schizophrenia.

and, rarely, manifest tetany with its signs of over-sensitivity to stimulus, hyperplasia of the parotid, etc. In addition to this I have quite often observed achylia and achlorhydria, constipation or diarrhœa, and eosinophilia with secondary anæmia, but one of the commonest symptoms has been a gradually increasing illness and cachexia that sometimes reached a very marked degree. H. Zondek and L. Mayer found the metabolism of these patients normal. It is, however, reasonable to assume that, in many patients with disturbances of thyroid and pituitary, it might show grave anomalies.

I have often exhorted my students, when dealing with this syndrome, to look first, not at the condition of the skin, but at the general disease process, and to speak of " sclerodermic dystrophias ".

The question whether the pluriglandular disorders are primary to the sclerodermic and dystrophic process may be answered as follows. The inconstancy and protean variability of the endocrine symptoms make it clear that they are associated expressions of the same processes that cause the dystrophic anomalies in the skin and elsewhere. Here, as in the myoneuropathies, I suspect that the cause lies in a primary lesion of the mesencephalic centres. It must be recognized, however, that some disease-forms — genito-sclerodermic dystrophy, for instance (Von Noorden)—are nowadays regarded as due to genuine primary pluriglandular insufficiency, and the sclerodermic processes with which they are associated as more or less subordinate. There is always the possibility, of course, that the sclerodermia is genuine and referable to a primary endocrine basis. However, on account of the present uncertainty of the nosological boundaries, the differential diagnosis is in many cases difficult or even impossible.

Treatment.—The endocrine symptoms of sclerodermia are important in planning treatment, for they may indicate which organic preparations it will be most profitable to exhibit. They are seen fairly often, though not quite so commonly, in other vasomotor and trophic diseases, especially Raynaud's disease and erythromelalgia.

There are a number of other constitutional and congenital disorders in which endocrine dysplasias are observed, or in the course of which endocrine anomalies appear, but the endocrine components are not so constant or numerous as in the conditions that have been named. Without going into details, I will mention the numerous chronic arthritic processes of endogenous origin, diabetes, gout, and diseases of the blood. For example, endocrine symptoms are fairly common in *familial hæmolytic jaundice*. I had a case with pluriglandular insufficiency of the thyro-genito-pancreatic type, and have observed a fair number of cases of hypogenitalism and infantilism with a strikingly spare but quite well-proportioned bone development. It is a reasonable inference that the infantilism in these cases is due to the impairment of the maturing processes by the hereditary condition. *Constitutional and familial polycythæmia* are sometimes associated with infantilism, hypogenitalism, goitre formation, lordosis and the like (Engelking). In these cases the blood-anomaly, by delaying their ripening process, is probably the cause of the infantilism and hypogenitalism.

Nevertheless, these examples afford no proof that gross disturbances of the endocrine glands and their relations one with another play any significant part in the production of the essential blood-conditions, as Naegeli and others have recently suspected. This theory is not supported by any convincing anatomical and experimental evidence, and can therefore as yet be of no substantial assistance in treatment.

Osteomalacia

Osteomalacia, or softening of the bones, is a disorder of the mineral metabolism the nature of which is still obscure. It is a comparatively rare disease ; its incidence varies in different places and from time to time, and it attacks women much more frequently than men. The ratio is said to be as 10 to 1, but this suggests that the diagnosis is missed more often in male patients. The morbidity, especially of the non-puerperal form, is much higher in South Germany, Austria, Switzerland and other southern countries than it is,

for example, in North Germany. The following forms may be distinguished :

i. The puerperal form, probably the commonest.

ii. Involutional and senile osteomalacia, also common if sought.

iii. The non-puerperal form, occurring in adults of all ages with hypoplasia, deficiency, chronic mental disorder, hypogenitalism and other constitutional conditions of pluriglandular insufficiency.

iv. Bone disease caused by starvation ; during the years of hunger and scarcity this form was very common among the young and old. In old patients, and especially women, it conformed closely to the clinical picture of osteomalacia, and in adolescents to that of late rickets.

The only symptomatic difference between these forms is that the familiar pelvic changes associated with puerperal osteomalacia are hardly ever seen in old patients and never at all in the non-puerperal form.

Symptoms and Course.—Osteomalacia shows itself clinically by *pain* in the back, all over the chest, and in the flanks, pelvis and thighs ; the onset is slow and insidious, but the disease eventually becomes very severe. The pain, which occurs spontaneously, reflects the abnormal sensitivity of the *bones* to pressure and impact, especially the ribs, sternum, pelvis (particularly the symphysis) and the whole vertebral column. The pain in the ribs on coughing or sneezing is often sufficient to justify the diagnosis. Very soon the patient acquires a waddling gait, a " duck walk ", which is originally adopted to spare his pain but which, through changes in the bones and joints, becomes a genuine paralysis or defect of stance. In puerperal osteomalacia the pelvis develops the well-known "ace of hearts" shape with a rostrate and projecting symphysis ; the result is a badly deformed and narrow pelvis. In pregnant women the lumbar vertebræ and femora are especially liable to be affected. In this form of osteomalacia, as in the others, the involvement of the sternum always leads to a marked kyphosis and a shortening of the trunk. The costal arches make direct contact with the sacral hollow of the pelvis, and this leads to the familiar

epigastric sulcus and to the patient's discovery—startling to him and his associates alike—that he is getting shorter. When long dresses were still worn, women patients used to complain that they were always treading on the hem of their skirts. The pains are so bad that, as the weeks and months go on, walking and standing become quite impossible. Nevertheless, careful examination shows that true muscular paralyses are rare, and that the predominating factor is the immobility caused by pain. The contraction of the adductors, which is often observed, is, in my opinion, a reflex product of the pain. *Muscular atrophies* of a degenerative kind, sensory disorders of nervous origin, and anomalies of the reflexes hardly ever appear. Trophic changes in the skin (such as atrophy and Recklinghausen's disease), hair and nails, and other vegetative nervous stigmata dependent on the endocrine system, are not uncommon. These endocrine symptoms, which, as we shall see, may often have a pathogenetic significance, are encountered much more often than used to be recognized. In the osteomalacia of pregnancy and the puerperium—the commonest form—typical hyperthyroidic disorders are found with extraordinary frequency (Hoennicke) ; I have found that the same applies to senile and pre-senile osteomalacia, which may be associated with classical Graves' disease. I have also repeatedly found, in non-puerperal osteomalacia, conditions such as myxœdema and adiposis dolorosa, which must be put down to defective and disordered thyroid function. Tetany and its stigmata are very common in all forms, expecially the puerperal and the starvation osteopathy. Finally, Bossi and others have seen defective function of the *chromaffin system*, and I have described cases of non-puerperal osteomalacia who showed pronounced disorders—amenorrhœa, adiposity, tetany, myxœdema and symptoms of Graves' disease. It is well known that psychical changes may accompany the myxœdema ; they seem to me to be conditioned by the state of the thyroid. When the features of Graves' disease are predominant they take the form of excitement and excess of affective tone ; in thyroidal deficiency the mental state tends to be dull and apathetic.

Metabolic changes occur, but observations on the retention and excretion of calcium and phosphorus have given very divergent results. There is no evidence that increased excretion and diminished retention are constant. The rise in the blood-calcium which is usually found seems to indicate that the bones are unable to fit the calcium which is conveyed to them. Nor is there any agreement in the results of the tests performed on nitrogen-metabolism. In pure osteomalacia the gas-interchange appears to be normal, but the basal metabolic rate is often very high or very low; this is probably because of the element of thyroidal disturbance which is so common in these patients.

Blood-changes are sometimes observed, usually in the direction of polycythæmia or of myelocytosis and eosinophilia (Naegeli). In non-puerperal cases I have always found a marked lymphocytosis, sometimes as much as 60 per cent, but the rest of the picture has been normal. In the later stages I have seen secondary anæmia.

The *bones*, especially those of the trunk, look very transparent under X-rays and are extremely pliable and brittle; but fractures are not very common. The calcium content is very low. They undergo on the one hand atrophy of the bone substance and on the other an abnormal proliferation of tissue with a low calcium content. The medullary canal in the long bones is consequently increased in section; the reticulations of the spongy part become coarse and transparent, and the compact part of the bones becomes extremely thin (H. Zondek). An atrophic and a hypertrophic form of osteomalacia have been distinguished on histological grounds. In old patients I generally found signs of the atrophic form.

Pathogenesis.—The accepted explanation of osteomalacia is that, in spite of a plentiful supply of calcium both in the blood and at the centres of ossification, the bones have become incapable of fixing and using it. The cause of this failure is referred to the endocrine system. Fehling believed that the osteomalacia of pregnancy and the puerperium was associated with an excessive ovarian function, and adduced the curvature effect of castration. Hoennicke and I have

concluded, from the frequency of thyroid symptoms in puerperal and non-puerperal senile osteomalacia respectively, that the thyroid gland plays a part ; its effect on bone growth is already recognized. In addition to this the frequency of parathyroidal stigmata (tetany) suggests that the parathyroid, which is known to control the calcium metabolism, is also a causative factor. The defective working of the chromaffin system has also been incriminated for similar reasons.

The *symptoms* are referable to so many glands that it is difficult to say which is responsible for the failure in the calcium deposition. One thing seems to me quite clear, and that is that there is no longer any justification for clinging to the narrow theory of excessive ovarian function. It has been suggested that the site of the disorder is in the metabolic centres of the mid-brain. Some investigators hold that the endocrine symptoms are associated and secondary to the bone changes, but to my mind this theory lacks foundation.

According to Fehling the **treatment** of osteomalacia occurring in pregnancy is castration, and Seitz reports cure by this means in 87 per cent of cases. Nevertheless, male senile and amenorrhœal female patients, in whom there is certainly no question of gonadal hyperfunction, have also apparently been cured. For these cases I prefer to order a long period of rest and a course of cod-liver oil with phosphates in rather large doses. I give a teaspoonful of a solution of phosphorus, 0·02 grm. in ol. jecoris aselli 100, twice or three times a day for some weeks or even months.

Osteomalacia patients usually tolerate these doses well. Other preparations of phosphorus do not seem to be so effective. Artificial sunlight treatment is also recommended. Organic preparations, such as adrenalin and pituitary extract, have not been so thoroughly tested. Adrenal injections of $\frac{1}{4}$-$\frac{1}{2}$ c.cm. of the stock solution may, however, be tried when phosphorus cannot be given, but should be rigorously avoided in patients with symptoms of hyperthyroidism and tetany.

The **prognosis** of puerperal osteomalacia is on the whole good if castration, or its new substitute, X-ray sterilization, is performed promptly. I have usually obtained good results in non-puerperal and senile osteomalacia, with complete restoration of function and cessation of pain, by treatment with phosphorus and rest.

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